Lung and pleural tumors

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Ibrahim Zardawi MD

Bachelor of Medicine, Bachelor of Surgery (MB ChB) University of Baghdad, Iraq, Master of Science in Pathology (MSc) University of Baghdad, Iraq, Fellow of the Royal College of Pathologists of Great Britain, Fellow of the Royal College of Pathologists of Australasia, Fellow of the International Academy of Cytology, Diploma in Cytopathology, Royal College of Pathologists of Australasia, Founding Fellow of the Faculty of Science of the Royal College of Pathologists of Australasia, Fellow of the College of the American Pathologists FCAP, Fellow of the American Association of Clinical Pathologists, Diploma of the European Board of Pathology

Lung cancer		
Year	Survival rates	Reason
1970 2000 2020 Current	10% 15% 20% 25%	Late diagnosis 25% of cases are diagnosed at an early stage 50% of cases present at late stage (survival rate of 9%) National 5-year survival average is 25%
2 million new lung cancer cases and 1.7 million deaths were recorded globally in 2020 The advent of targeted therapies guided by predictive markers heralds a promising future, with improved outcomes on the horizon		

Lung cancer exhibits a diverse biological landscape, ranging from highly aggressive to indolent growth, shaped by significant molecular and pathological variations that profoundly impact patient outcomes.

Lung cancer

Patient #. 1	Patient #. 2
63-year-old female Heavy smoker Clinical Features 3-week history of cough, hemoptysis, dyspnea Systemic: weakness, weight loss CNS: headaches, right-sided weakness and coordination deficits Physical exam: Decreased left-sided breath sounds Imaging Findings: Primary: Large left central lung mass (5.2cm) obstructing main bronchus Metastases: Brain (multiple lesions) Adrenal: 5cm right mass Mediastinal/hilar lymphadenopathy Diagnostic: Bronchoscopy confirmed obstructing tumor Biopsy obtained (small cell NE carcinoma) Outcome: Deceased 2 weeks after biopsy	63-year-old female Non-smoker Clinical Presentation: Short history of cough with minor hemoptysis Otherwise healthy and asymptomatic Physical exam: Normal vital signs Clear breath sounds No neurological deficits Normal abdominal exam Imaging & Diagnostics: CXR: 2.5cm right upper lobe mass Chest CT: 2.8cm spiculated mass, no lymphadenopathy Bronchoscopy: Right upper bronchus lesion successfully biopsied (adenocarcinoma) Treatment & Outcome: Received surgery and targeted therapy Excellent prognosis: alive and well at 5-year follow-up

Tumours of the lung
WHO Classification, 2021

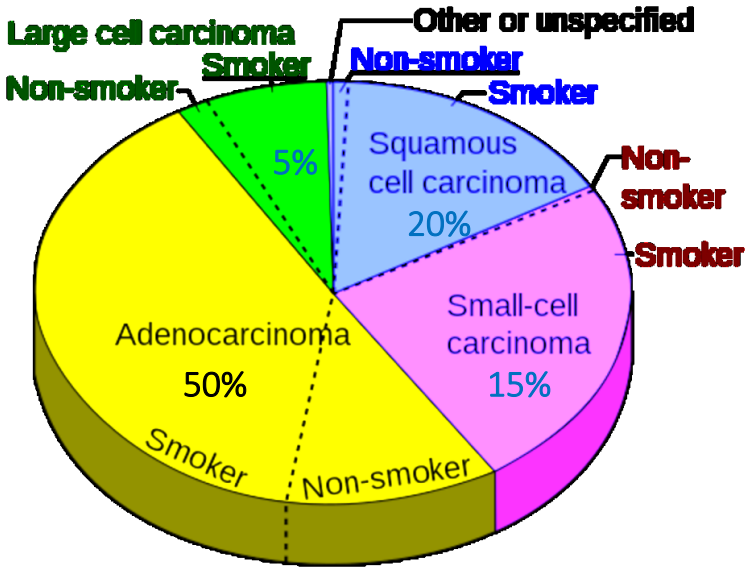
Adenomas
Sclerosing pneumocytoma
Alveolar adenoma
Papillary adenoma of the lung
Bronchiolar adenoma / ciliated muconodular papillary tumour
Mucinous cystadenoma of the lung
Mucous gland adenoma of the lung
Precursor glandular lesions
Atypical adenomatous hyperplasia of the lung
Adenocarcinoma in situ of the lung
Adenocarcinomas 50%
Minimally invasive adenocarcinoma of the lung
Invasive non-mucinous adenocarcinoma of the lung
Invasive mucinous adenocarcinoma of the lung
Colloid adenocarcinoma of the lung
Fetal adenocarcinoma of the lung
Enteric-type adenocarcinoma of the lung
Squamous precursor lesions
Squamous dysplasia and carcinoma in situ of the lung
Squamous cell carcinomas 20%
Squamous cell carcinoma of the lung
Lymphoepithelial carcinoma of the lung

Large cell carcinomas <5%
Large cell carcinoma of the lung
Adenosquamous carcinoma
Adenosquamous carcinoma of the lung
Sarcomatoid carcinomas
Pleomorphic carcinoma of the lung
Pulmonary blastoma
Carcinosarcoma of the lung
Other epithelial tumours
NUT carcinoma of the lung (see NUT carcinoma of the thorax)
Thoracic SMARCA4-deficient undifferentiated tumour
Salivary gland-type tumours
Pleomorphic adenoma of the lung
Adenoid cystic carcinoma of the lung
Epithelial-myoepithelial carcinoma of the lung
Mucoepidermoid carcinoma of the lung
Hyalinizing clear cell carcinoma of the lung
Myoepithelioma and myoepithelial carcinoma of the lung
Lung neuroendocrine neoplasms 20%
Lung neuroendocrine neoplasms: Introduction
Precursor lesion
Diffuse idiopathic pulmonary neuroendocrine cell hyperplasia
Neuroendocrine tumours
Carcinoid/neuroendocrine tumour of the lung
Neuroendocrine carcinomas
Small cell lung carcinoma
Large cell neuroendocrine carcinoma of the lung

Tumours of ectopic tissues
Melanoma of the lung
Meningioma of the lung
Mesenchymal tumours specific to the lung
Pulmonary hamartoma
Pulmonary chondroma
Diffuse pulmonary lymphangiomatosis
Pleuropulmonary blastoma
Pulmonary artery intimal sarcoma
Congenital peribronchial myofibroblastic tumour
Primary pulmonary myxoid sarcoma with EWSR1-CREB1 fusion
PEComatous tumours
Lymphangioleiomyomatosis of the lung
PEComa of the lung
Haematolymphoid tumours
Haematolymphoid tumours of the lung: Introduction
MALT lymphoma of the lung
Pulmonary diffuse large B-cell lymphoma
Lymphomatoid granulomatosis of the lung
Intravascular large B-cell lymphoma of the lung
Pulmonary Langerhans cell histiocytosis
Pulmonary Erdheim-Chester disease

Tumours of the lung		
Epithelial tumors (carcinomas)		75%
Adenocarcinomas	~50%	
Squamous cell carcinomas	20%	
Large cell undifferentiated carcinomas	~5%	
Other carcinomas		
Neuroendocrine Neoplasms		~20%
Neuroendocrine **tumors** (carcinoid tumor)	~5%	
Neuroendocrine **carcinomas** (small cell, large cell)	15%	
Mesenchymal, lymphoid, other hematolymphoid tumours		~5%
Sarcomas, lymphomas, other tumors		

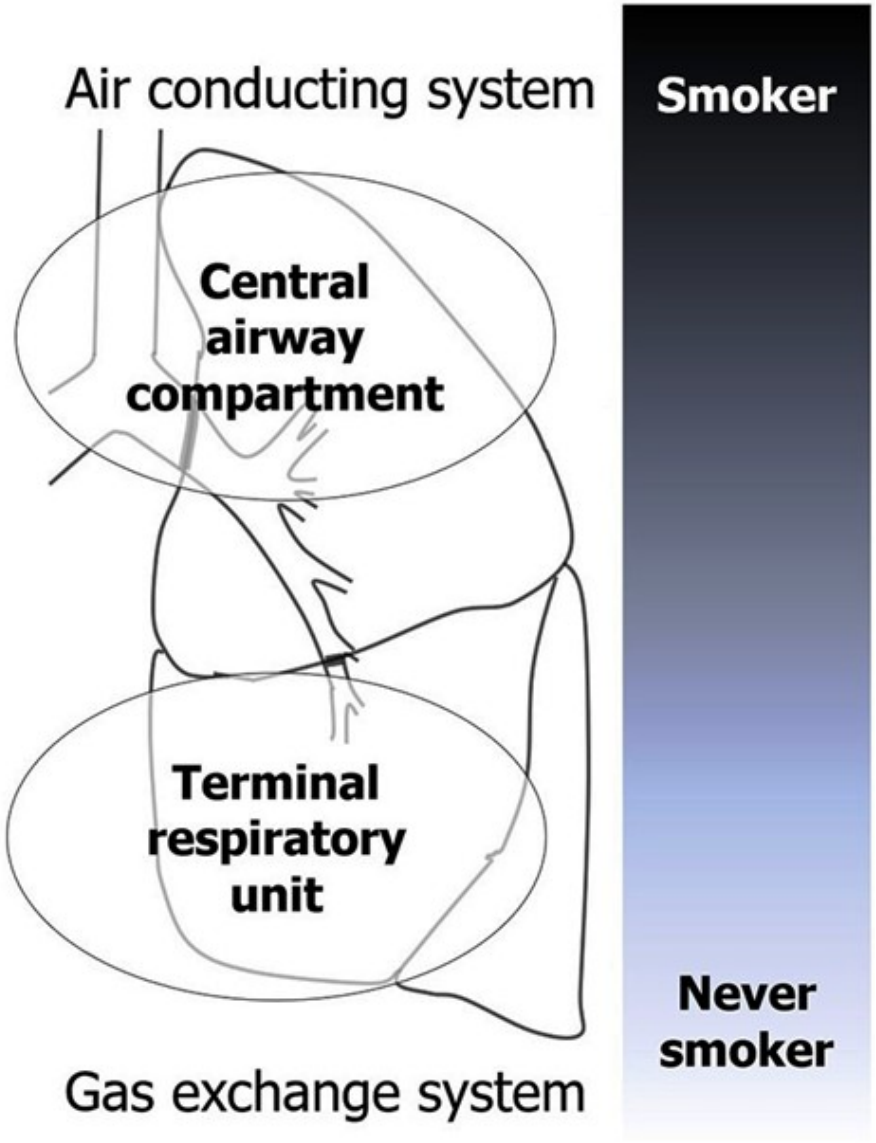
Smoking and lung cancer



Smoking is the most important risk factor involved in **>80%** of the cancers

Up to 20% of lung cancers occur in non-smokers (mostly in women; majority are adenocarcinomas with EGFR mutations; almost none have KRAS mutations)

Tumor location is an important prognostic factor



Majority of lung cancers in **smokers** arise **centrally** (air conducting system)

Central cancers are mainly **small cell carcinomas and squamous cell carcinomas**
EGFR generally not activated
KRAS commonly activated

Most lung cancers in **non-smokers arise peripherally** (gas exchanges system)

Peripheral cancers are mainly **adenocarcinomas**
Most are **EGFR activated**
Almost none are KRAS activated

Changes in frequency of histological types of lung cancer in the last 5 decades		
Tumour type	1977-1981	2012-2016
Squamous cell carcinoma (SCC)	>40%	<25% ⬇
Adenocarcinoma (ADC)	<30%	>50% ⬆
Small cell NEC (SCLC)	>20%	<15%
Large cell NEC (LCNEC)	<1%	5%
Large cell undifferentiated carcinoma NOS	10%	1%

Reasons for the epidemiologic shift

Change in cigarette construction and tobacco composition which lead to increased puff volume and shifted of carcinogen deposition to the periphery

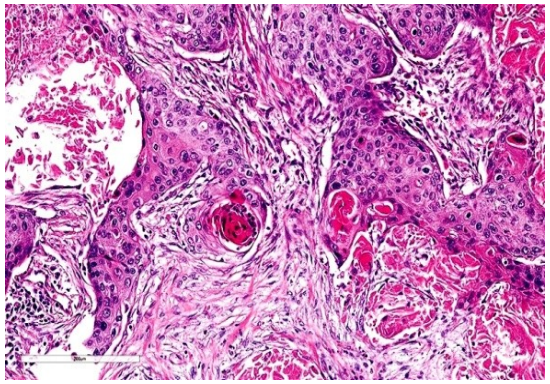
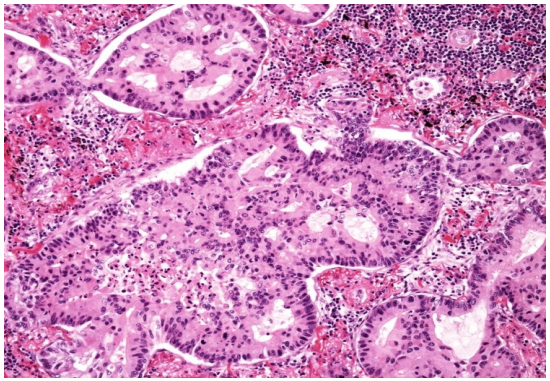
Declines in prevalence of smoking among males than females shifted the M:F ratio from 3:1 to 1:1

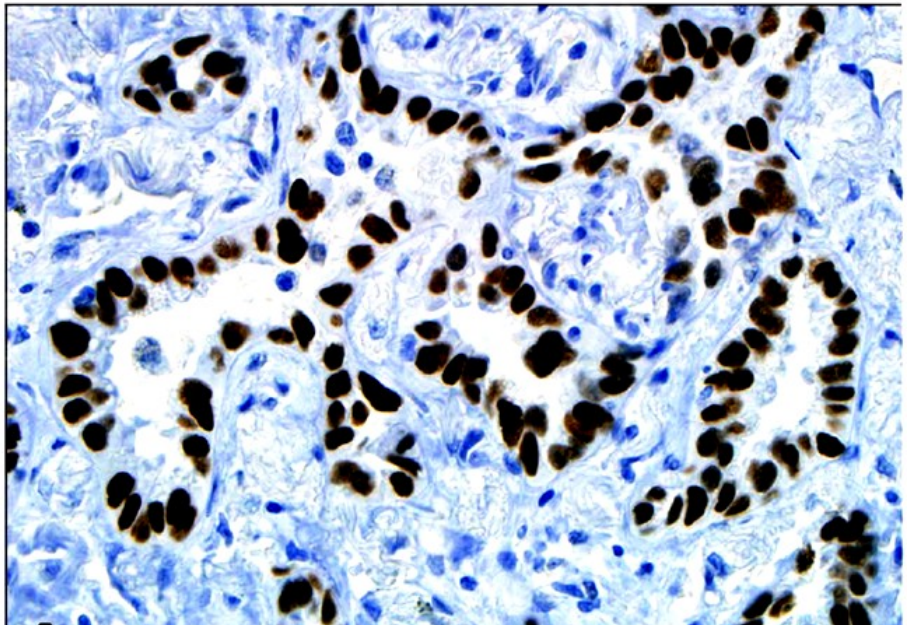
Improvement in histological diagnosis due to use of IHC and molecular testing has lead to refinement in diagnosis

Targeted therapy and use of **predictive markers** have lead to improved outcome

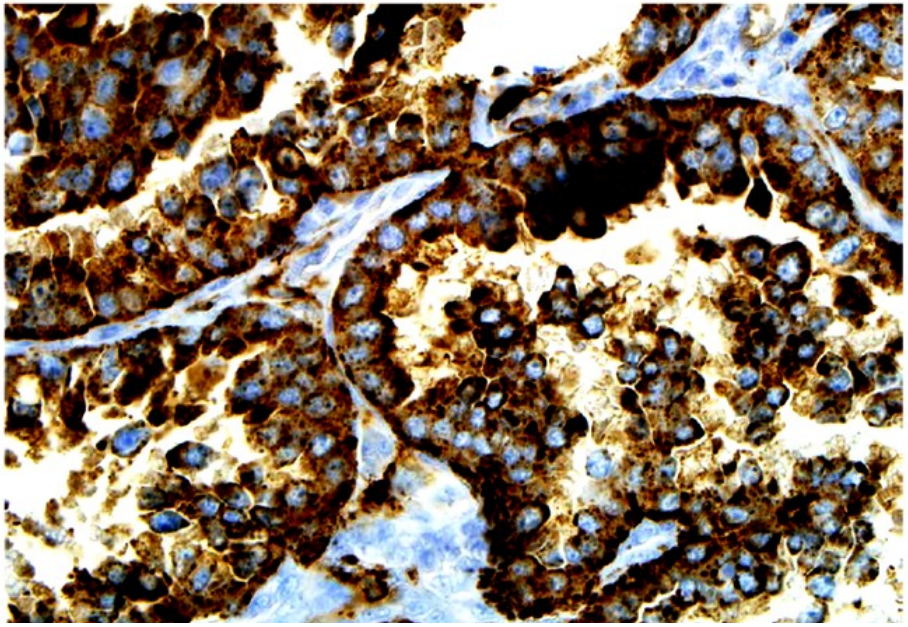
Lung cancer terminology in resection specimens and small samples	
Large specimens (resection and postmortem)	Small samples (FNA, core biopsies, etc)
Squamous cell carcinoma (SCC) (Keratin formation or intercellular bridges)	Squamous cell carcinoma Non-small cell carcinoma favor SCC
Adenocarcinoma (ADC) (Glands or mucin)	Adenocarcinoma Non-small cell carcinoma favor ADC
Neuroendocrine neoplasms (NEN) Neuroendocrine Tumor (NET) Neuroendocrine Carcinoma (NEC) Small cell NEC Large cell NEC	Neuroendocrine neoplasms (NEN) Neuroendocrine Tumor (NET) Neuroendocrine Carcinoma (NEC) Small cell NEC (SCLC) Non-small cell carcinoma (NSCC) with large cell neuroendocrine (LCNEC) features
Large cell undifferentiated carcinoma	NSCC NOS

IHC markers used in the evaluation of squamous cell carcinoma (SCC) and adenocarcinoma (ADC)

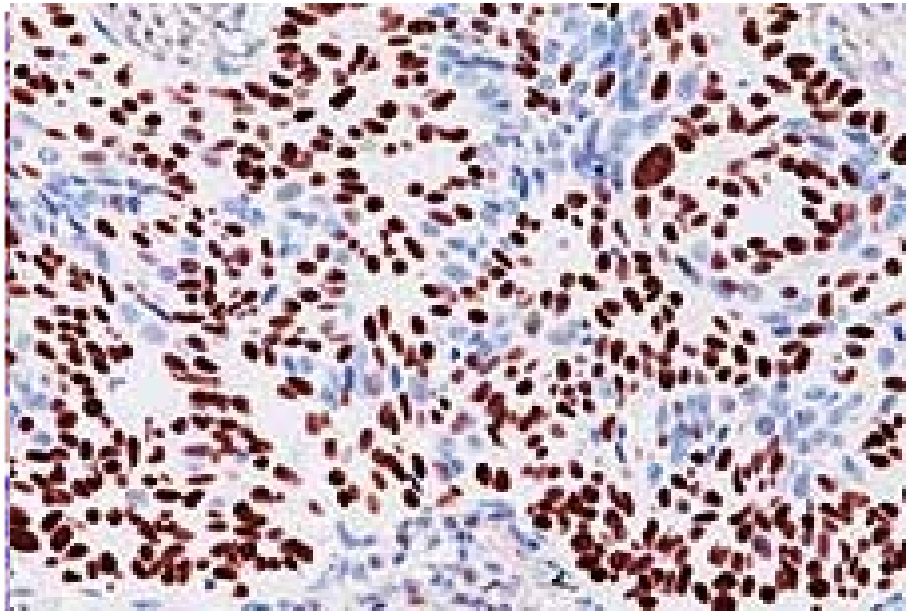
	SCC	ADC
Primary diagnosis is based on morphology Confirmed by IHC	Individual cell keratinization, keratin pearl formation, intercellular bridges	Gland formation, mucin production Tubular, papillary, lepidic, mucinous, solid, micropapillary
Morphology		
IHC markers		
TTF1 (Thyroid Transcription factor-1)	Neg	Pos
Napsin A	Neg	Pos
P40 (subunit of IL-12)	Pos	Neg
HMW cytokeratins (CK5/6)	Pos	Neg



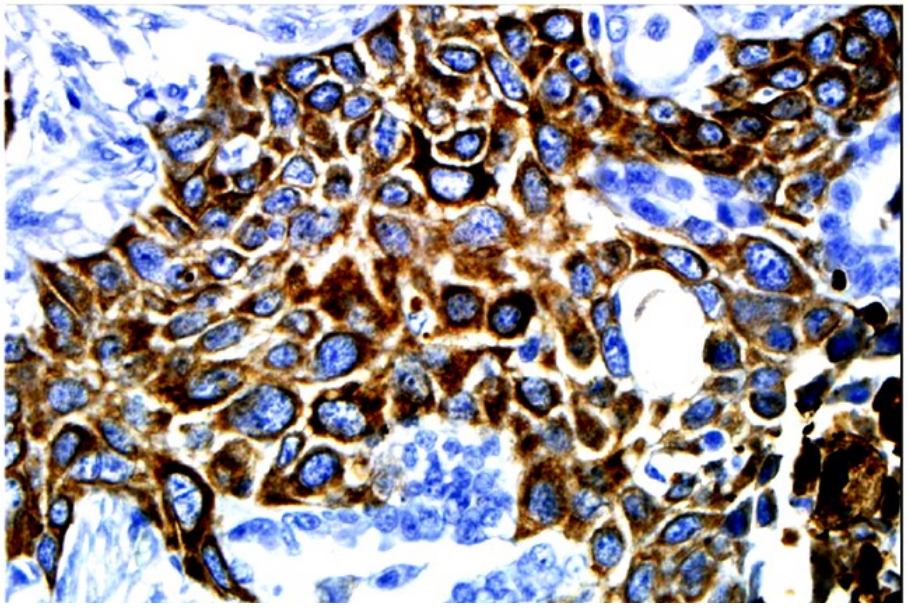
Adenocarcinoma, TTF1 Pos



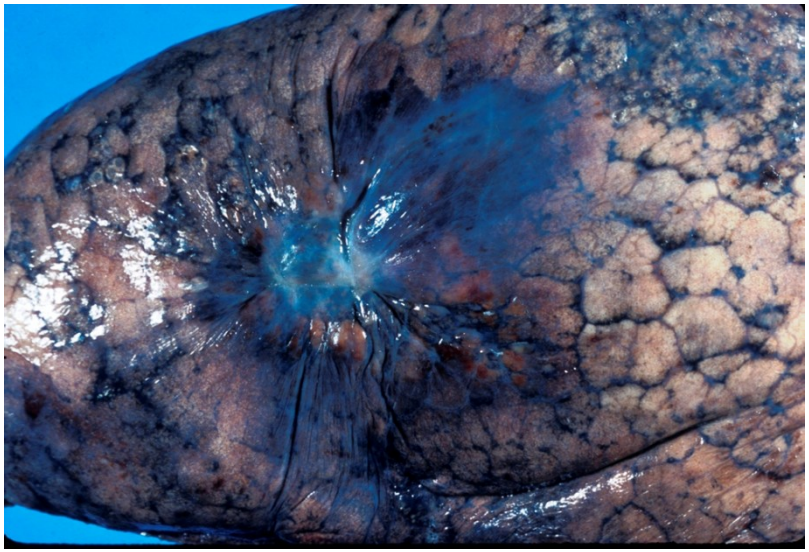
Adenocarcinoma, Napsin A Pos

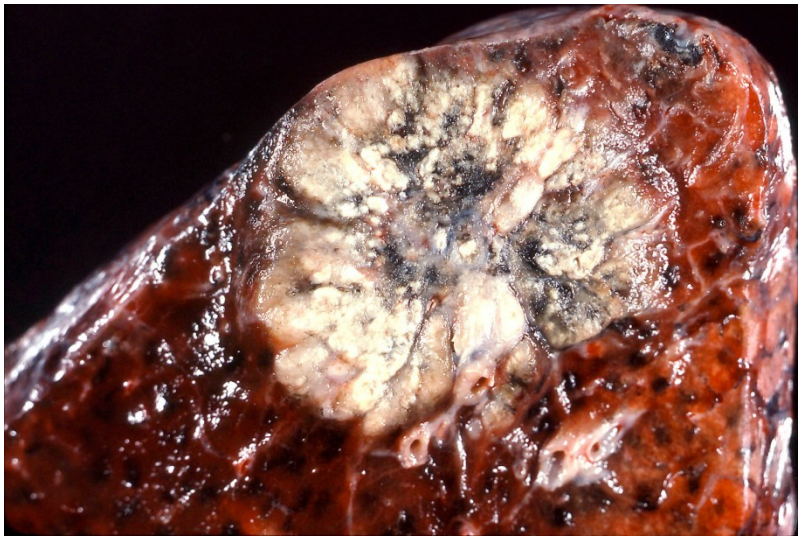


Squamous cell carcinoma, p40 Pos



Squamous cell carcinoma, HMW keratin Pos





Adenocarcinoma (ADC)

Gland forming tumour

Mucinous and non-mucinous subtype

Non-mucinous may show several histological patterns

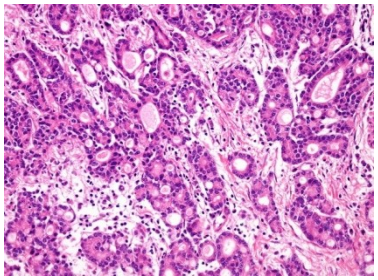
ADC cells are typically positive for Napsin A, TTF-1 and low molecular weight cytokeratin positive

Squamous markers (P40 and high molecular weight keratins CK5/6) are negative

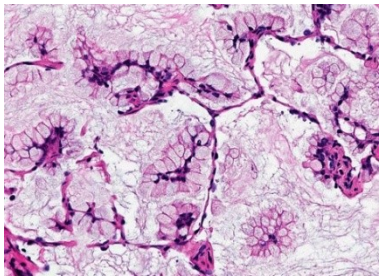
Napsin A is an aspartic proteinase expressed in lung and kidney
Marker for lung adenocarcinoma and renal cell carcinoma (RCC)

Adenocarcinomas display glandular differentiation and shows one or more **architectural features**

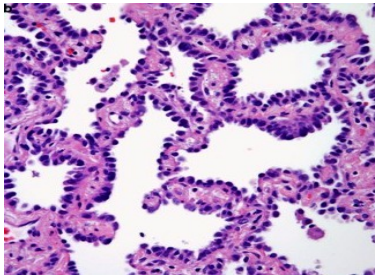
- Acinar
- Lepidic
- Papillary
- Mucinous
- Micropapillary
- Solid



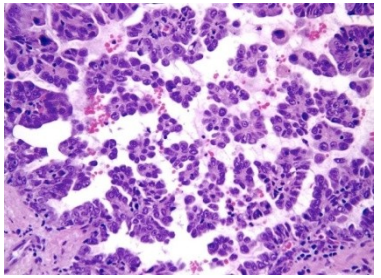
Acinar ADC



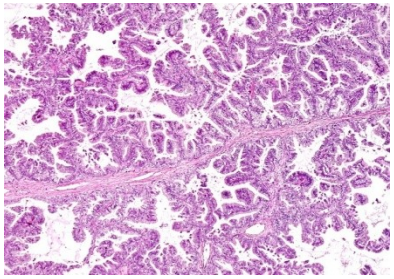
Mucinous ADC



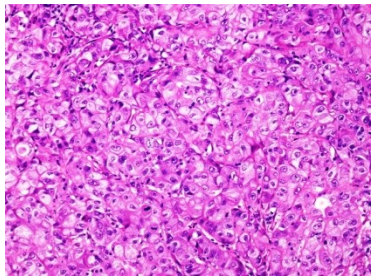
Lepidic ADC



Micropapillary ADC

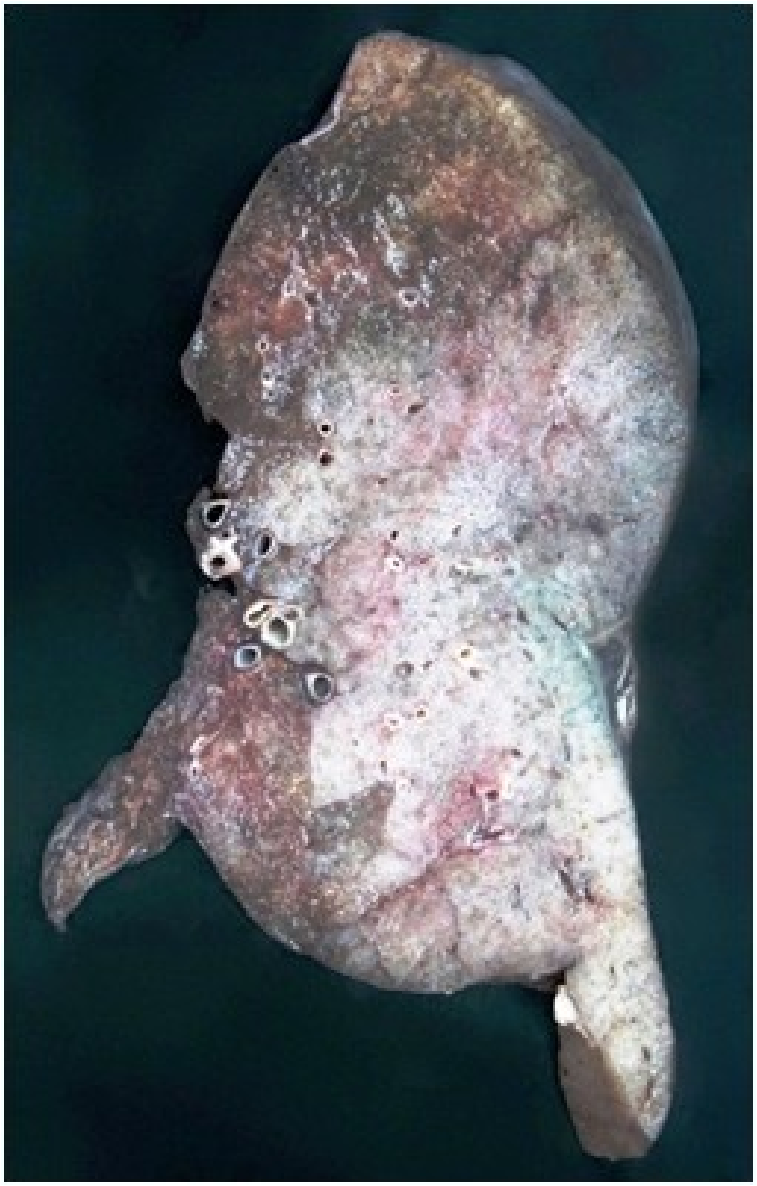


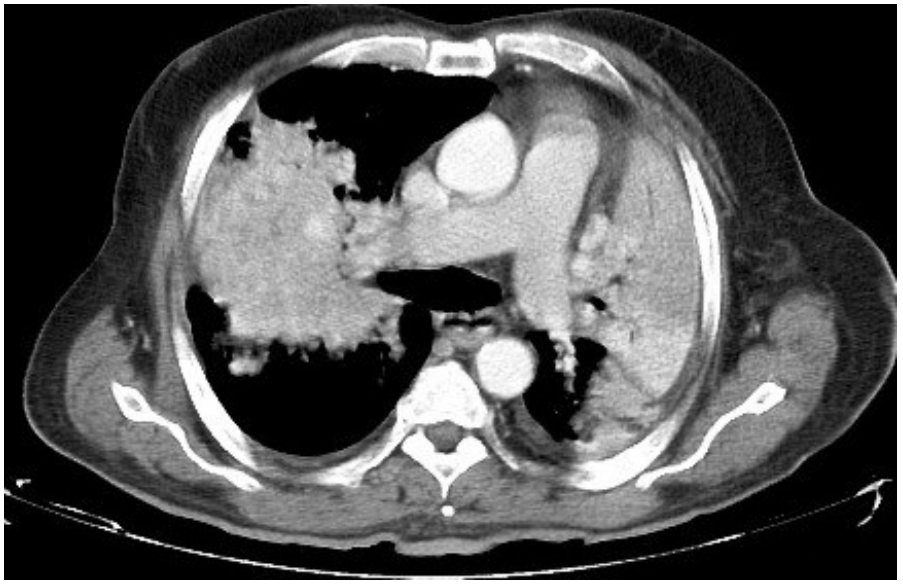
Papillary ADC

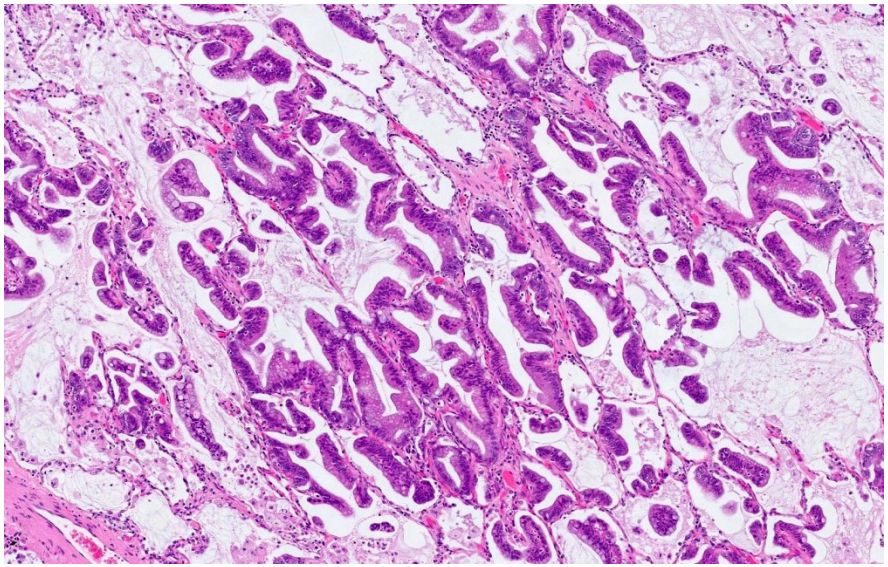


Solid ADC

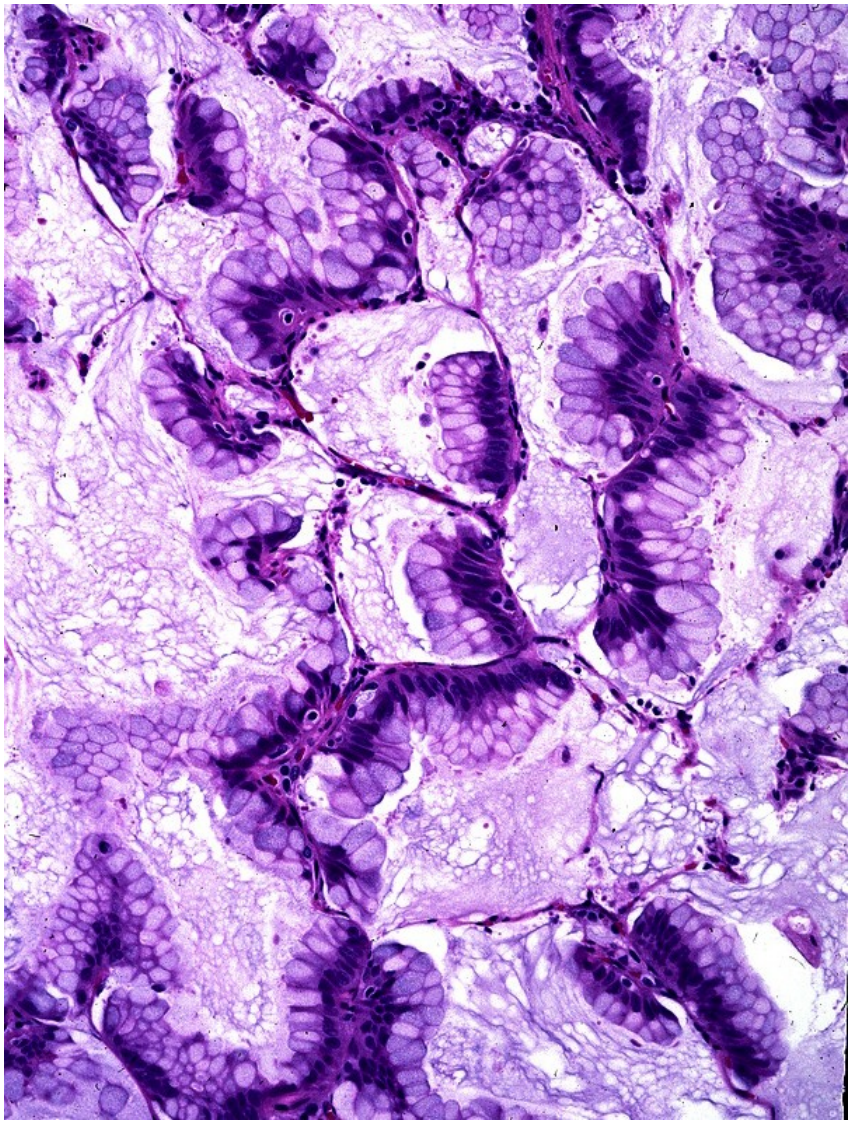
Mucinous adenocarcinoma

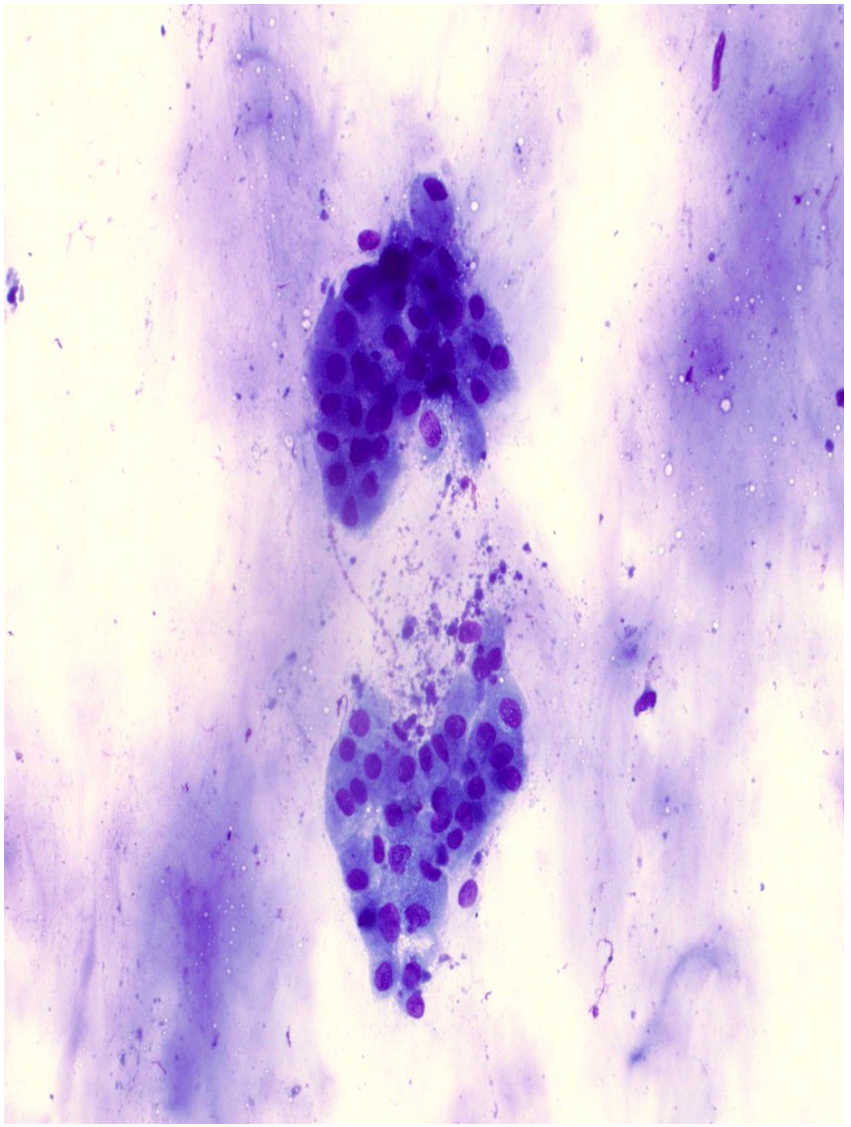




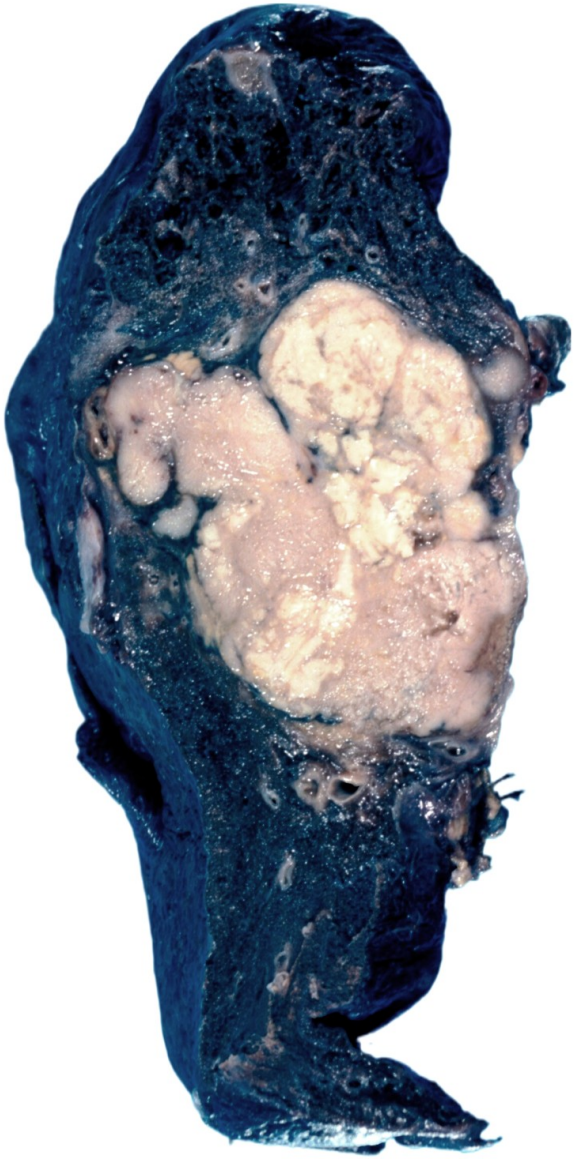


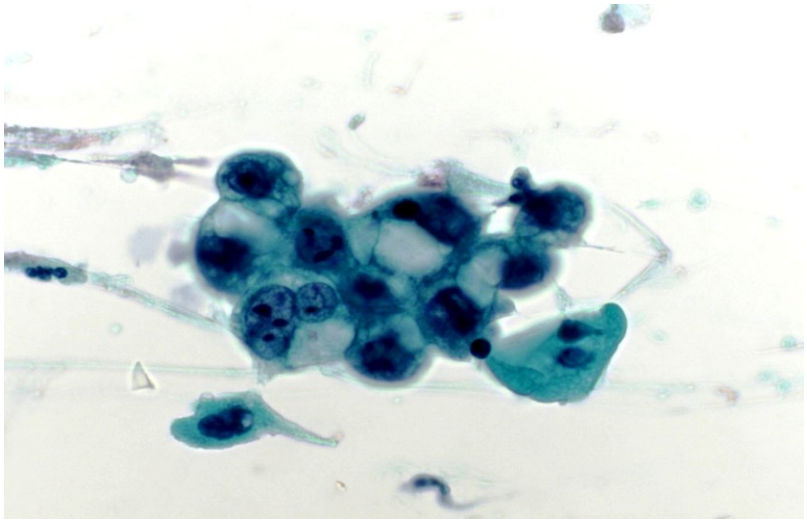
Mucinous adenocarcinoma

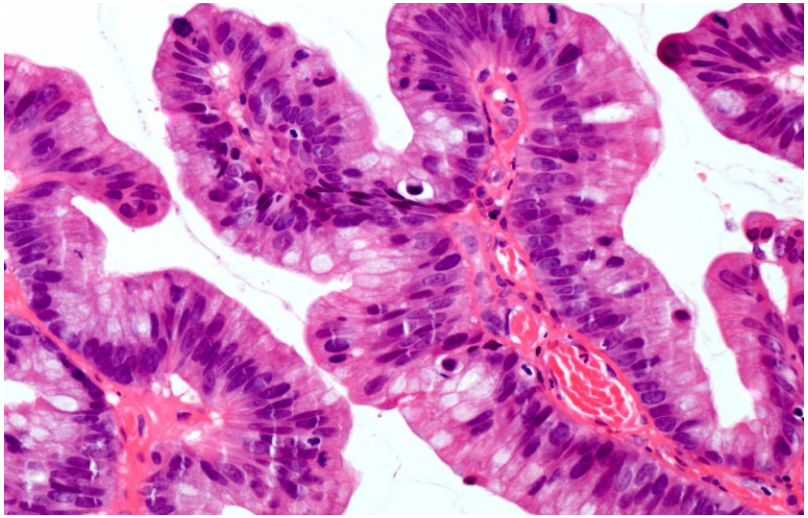




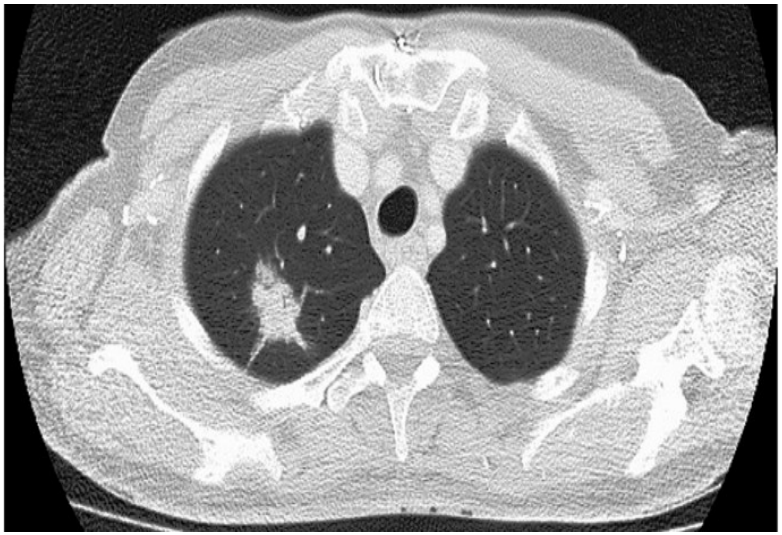
Non-mucinous adenocarcinoma (macroscopic, cytology and histology)

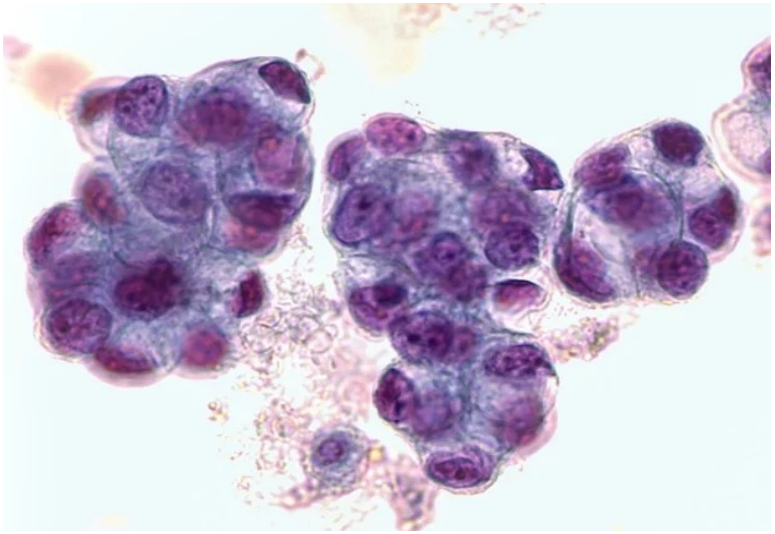


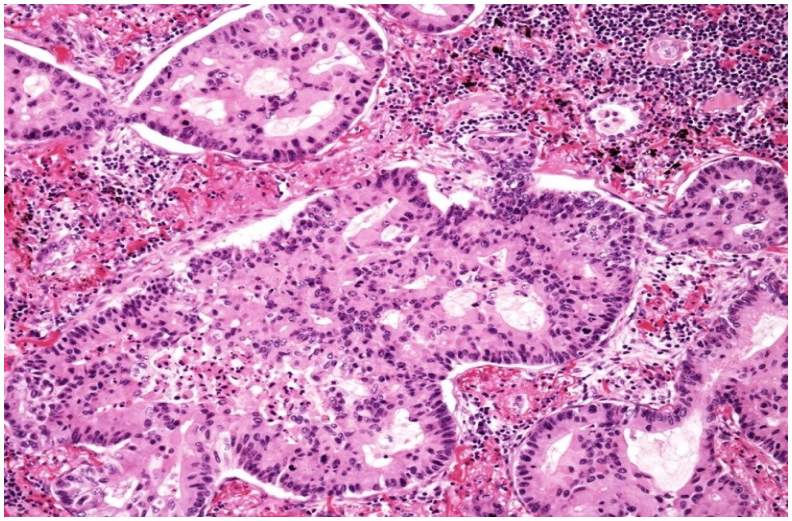


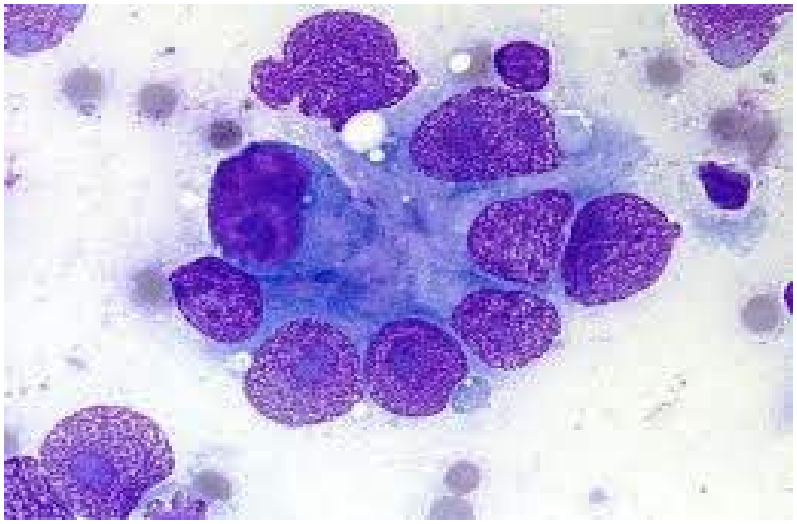


Non-mucinous adenocarcinoma

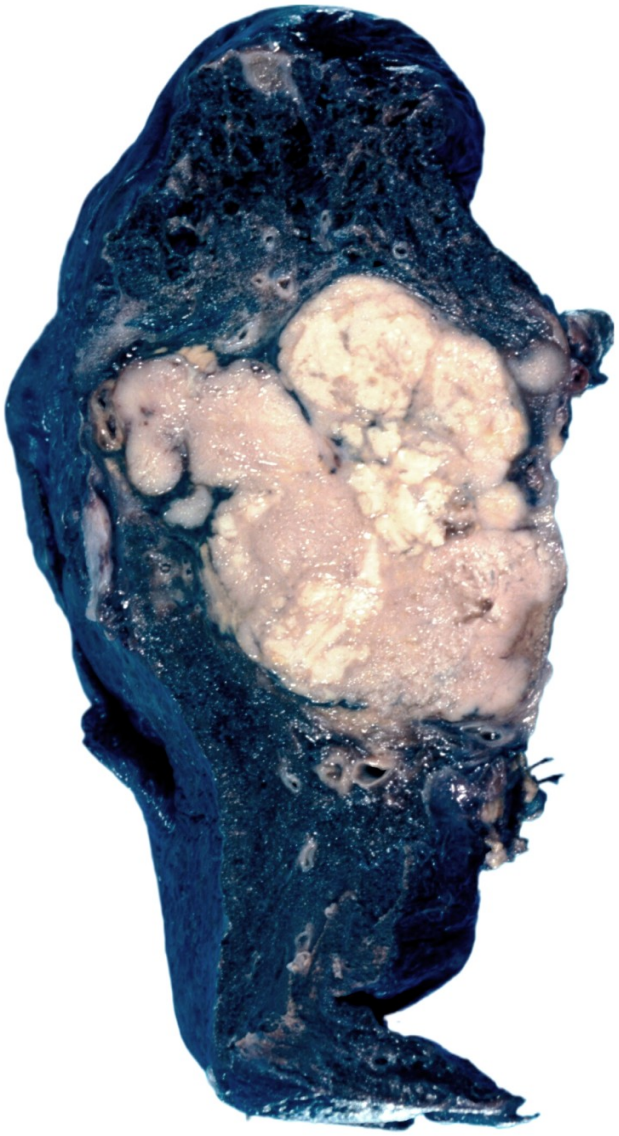




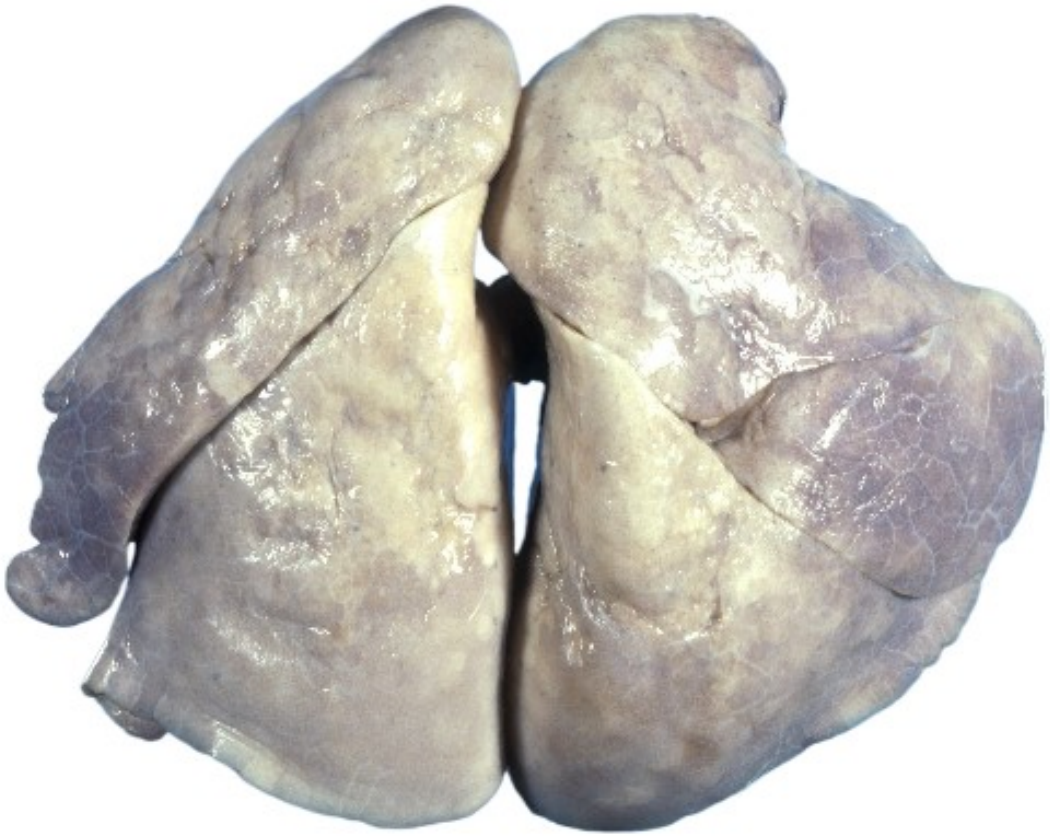




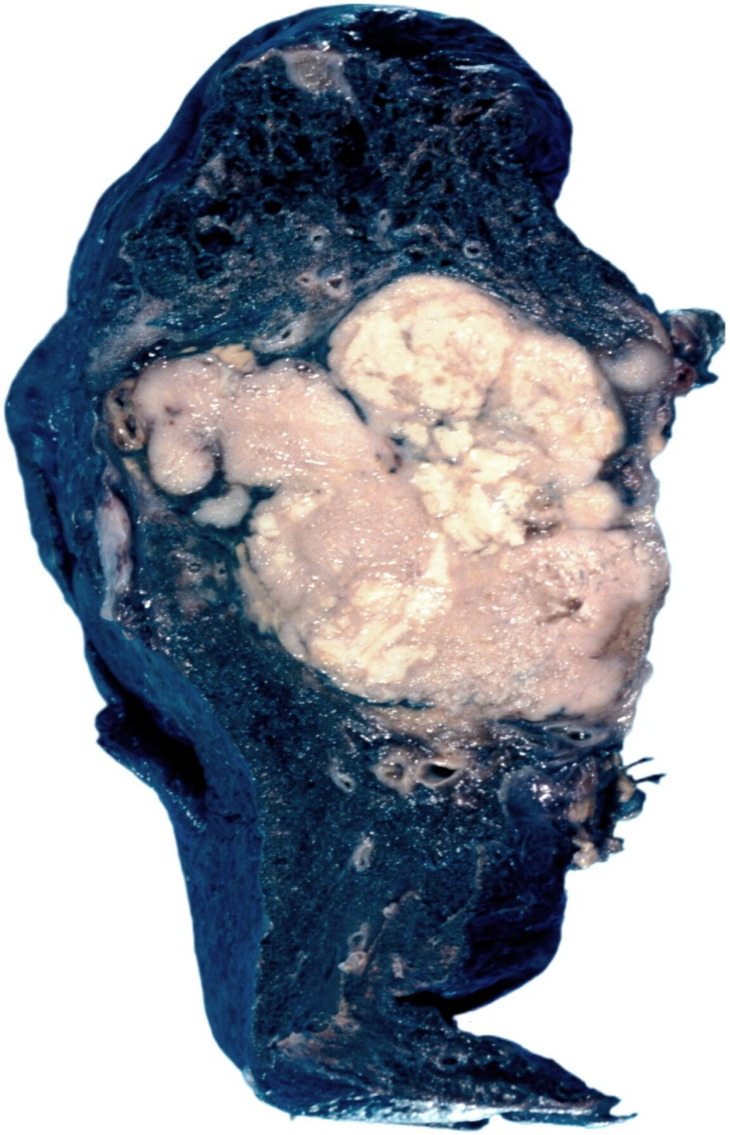
Black lung with non-mucinous adenocarcinoma



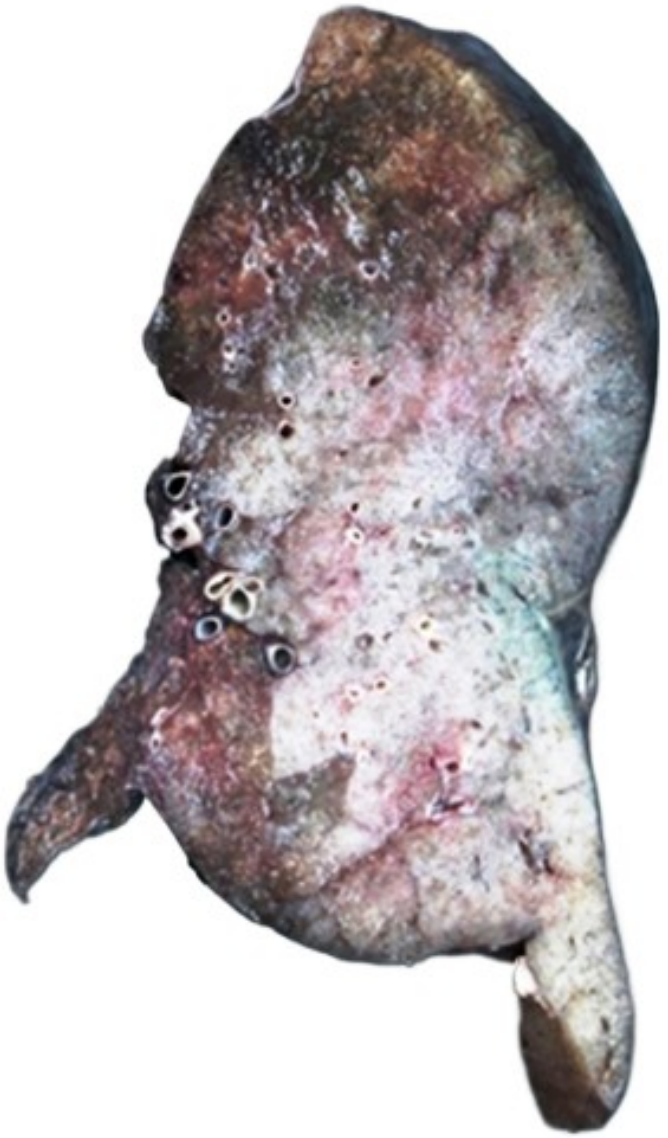
Normal lung



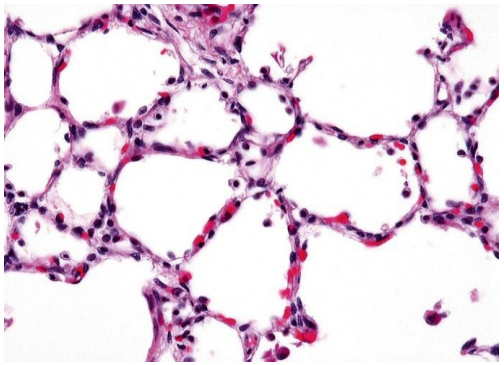
Non-mucinous adenocarcinoma



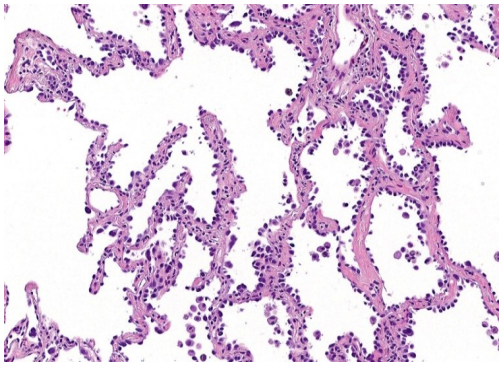
Mucinous adenocarcinoma



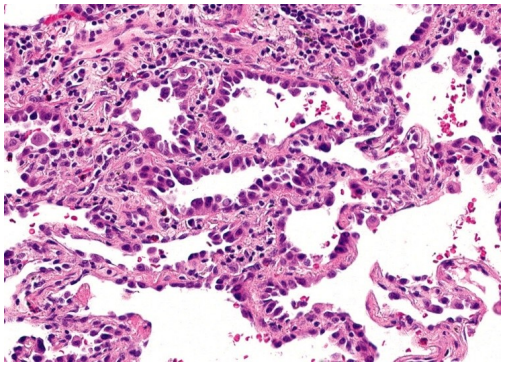
Pathway to lung adenocarcinoma (ADC) and precancerous lesions
Atypical Adenomatous Hyperplasia Small (<5mm) focus of atypical type II pneumocyte
Adenocarcinoma in situ Larger proliferation of atypical type II pneumocytes ≤30mm, without invasion
Minimally invasive adenocarcinoma Proliferation of atypical type II pneumocytes, ≤30 mm with invasive component ≤5mm
Invasive adenocarcinoma Invasive component is >5mm



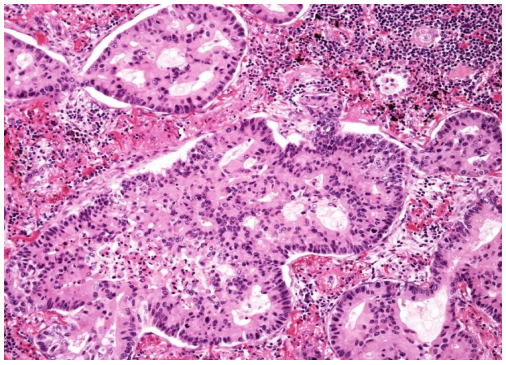
Normal lung parenchyma



Atypical Adenomatous Hyperplasia (AAH) <5mm

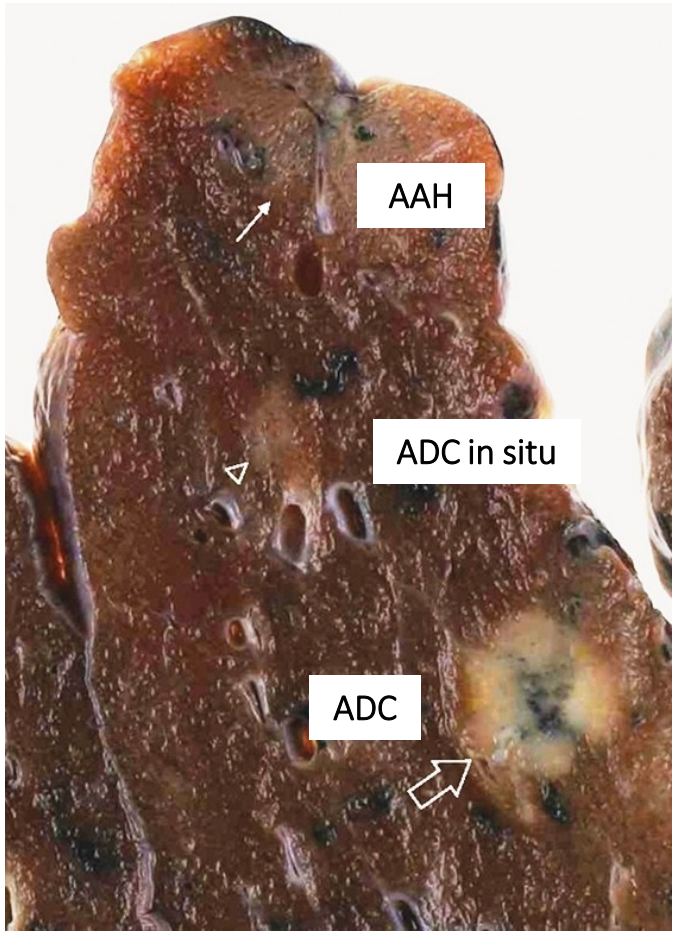


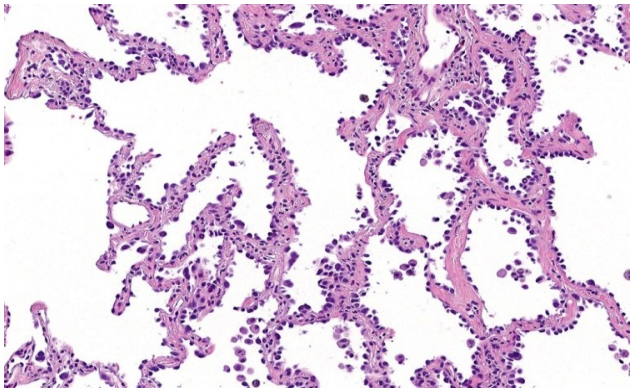
Adenocarcinoma in situ (ADC in situ)
≤30mm, without invasion



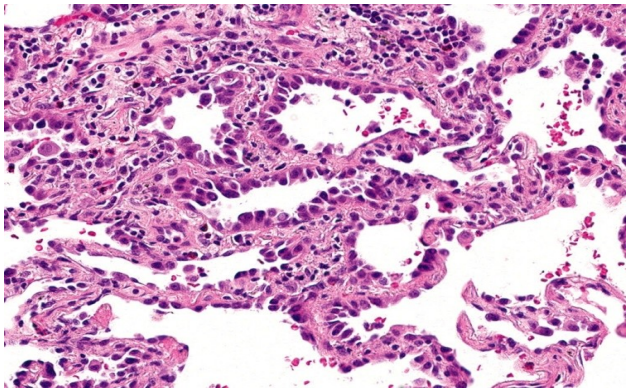
Invasive Adenocarcinoma >5mm

Adenocarcinoma and precursor lesions

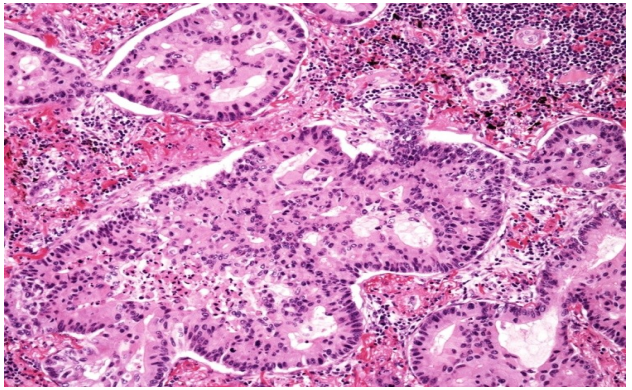




AAH (<5mm)



ADC in situ (>5mm to ≤30mm)



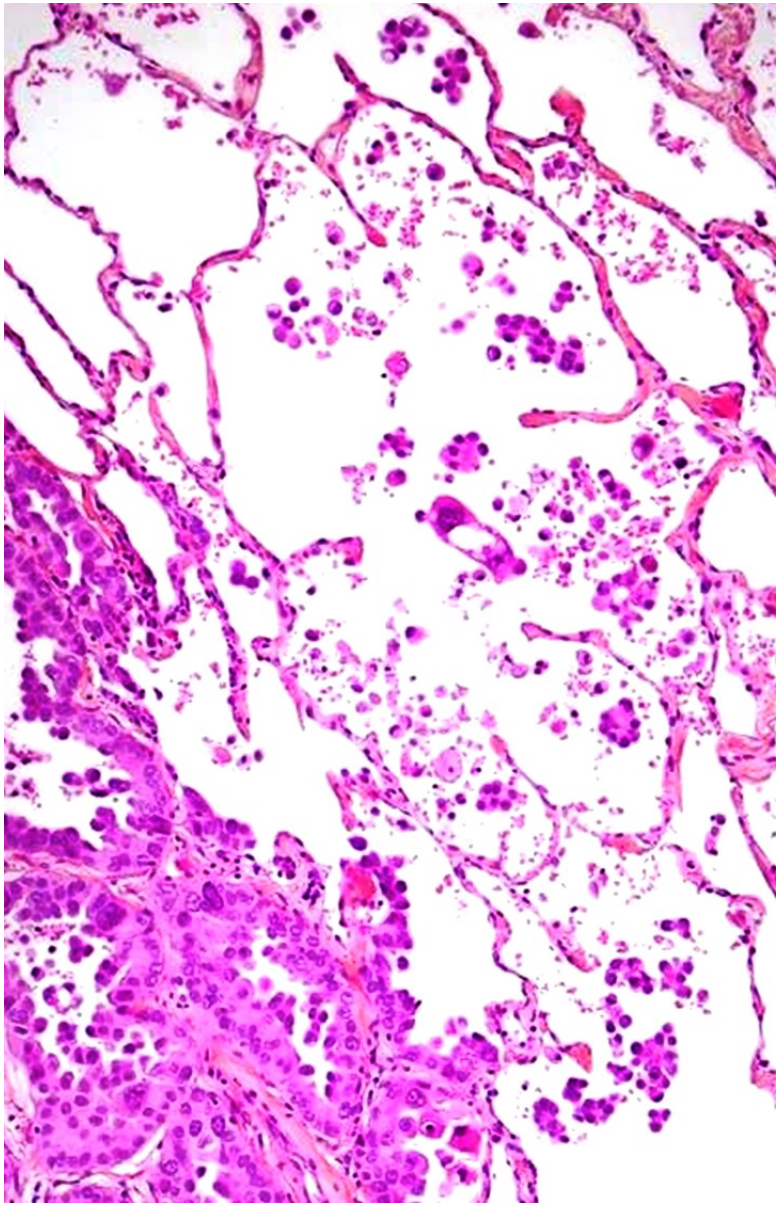
Invasive ADC

Adenocarcinoma summary

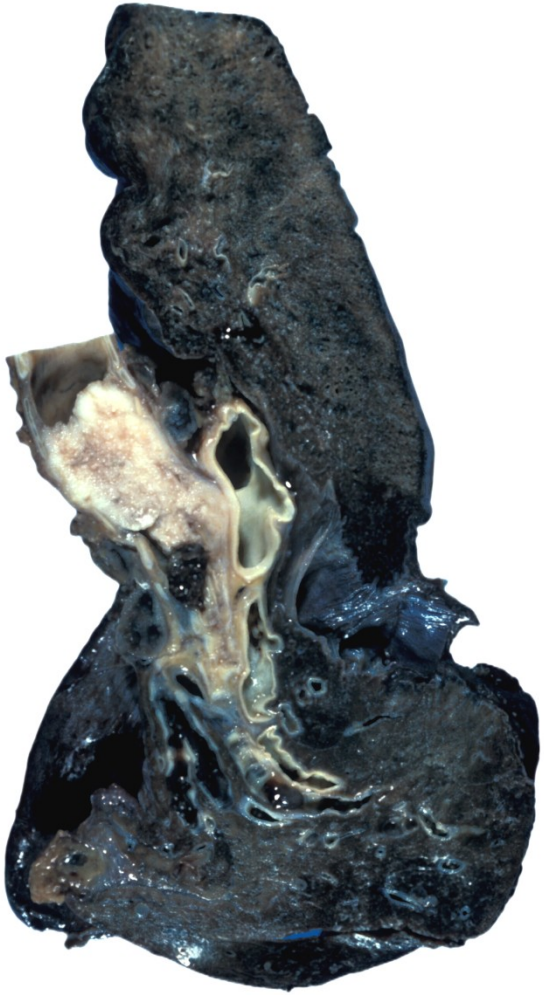
Often presents as a **peripheral mass** with gland formation and mucin production

Mucinous adenocarcinomas tend to **spread aerogenously**, forming satellite tumors (less likely to be cured by surgery)

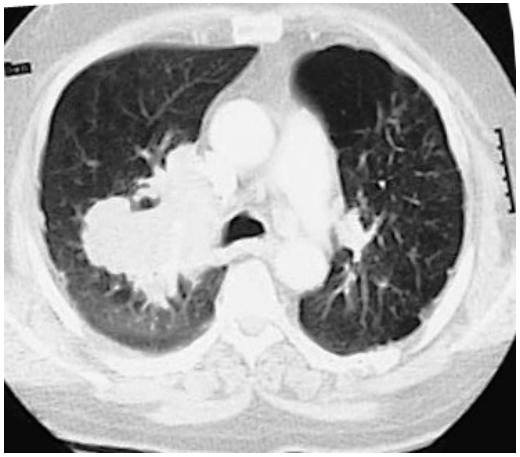
Oncogenic gain-of-function mutations occur in one third: **EGFR** in 15%, **ALK** in 5%, **ROS1** in 1%, **MET** in 2%, **RET** in 1%, **BRAF** in 2%, **PI3K** in 2% and **KRAS** in 30%

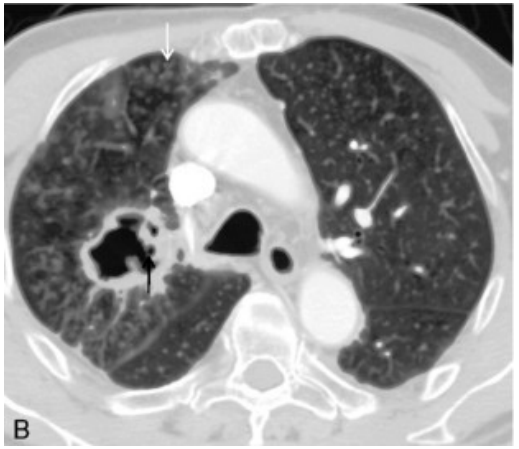


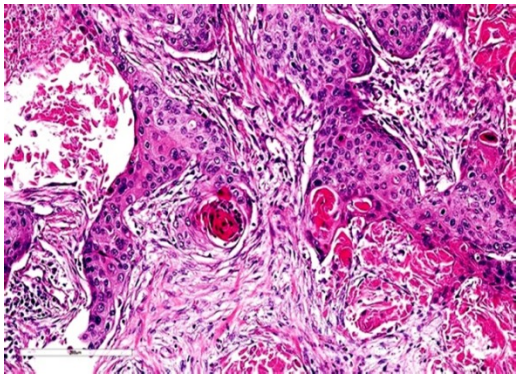
Squamous cell carcinoma

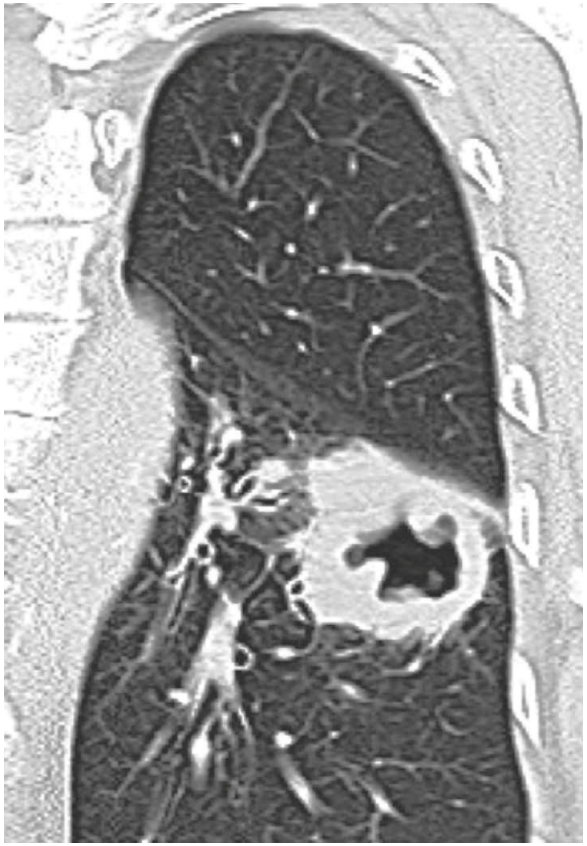


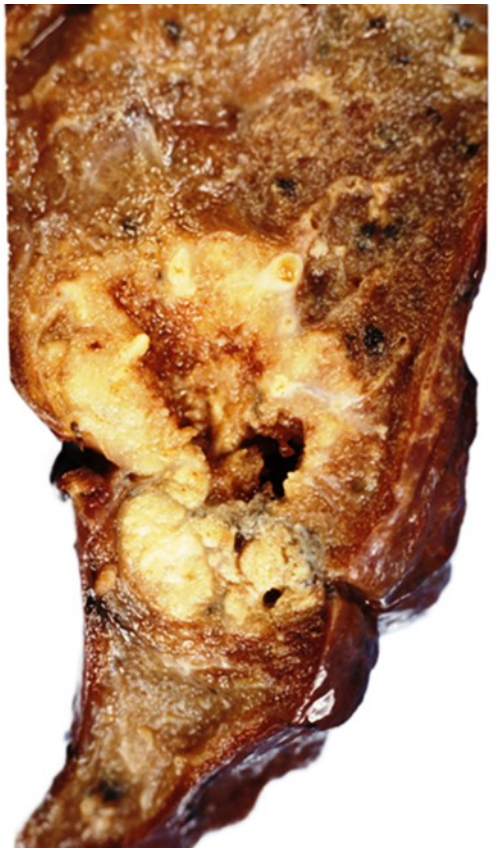
Squamous cell carcinoma



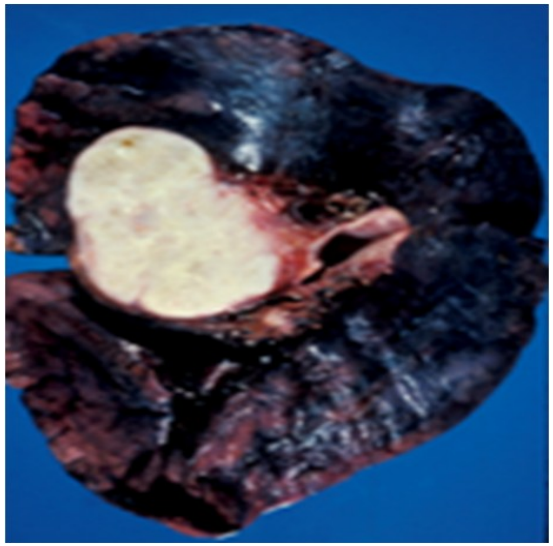


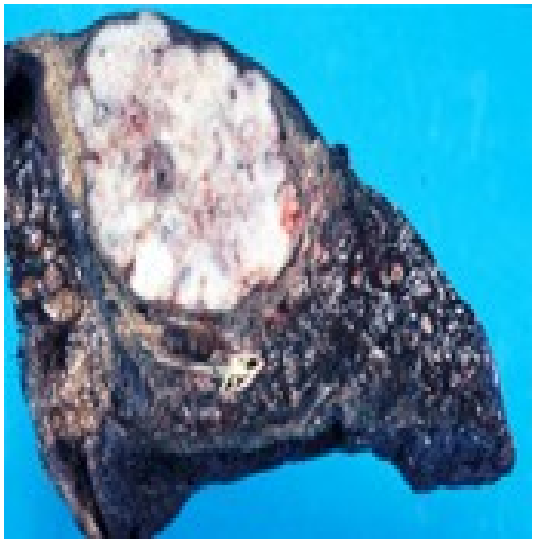


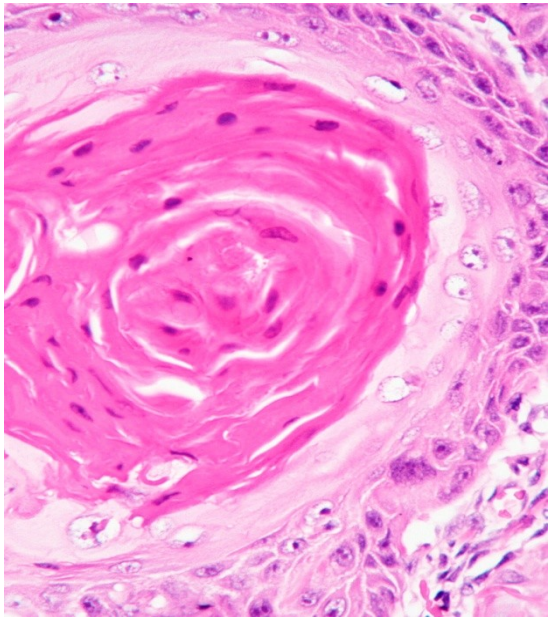


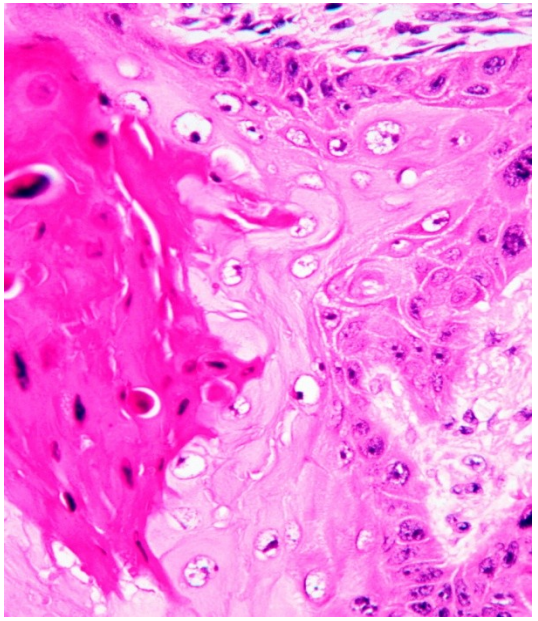


Squamous cell carcinoma

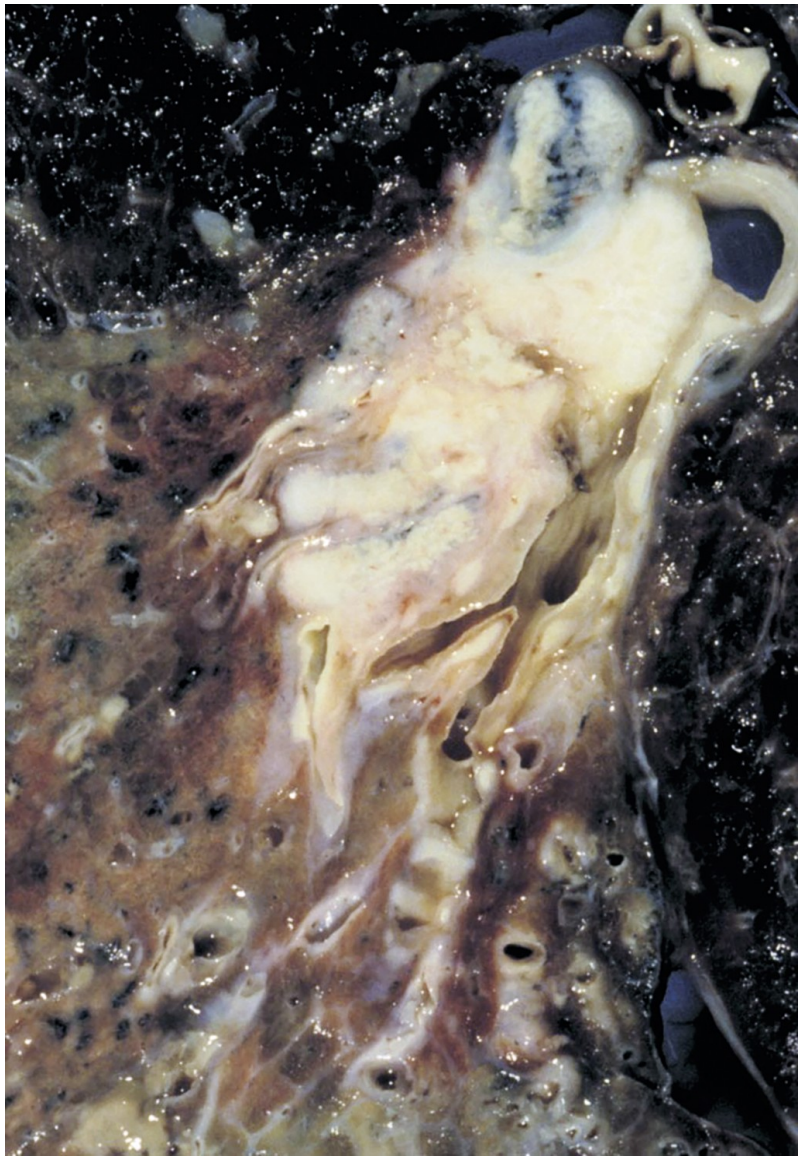


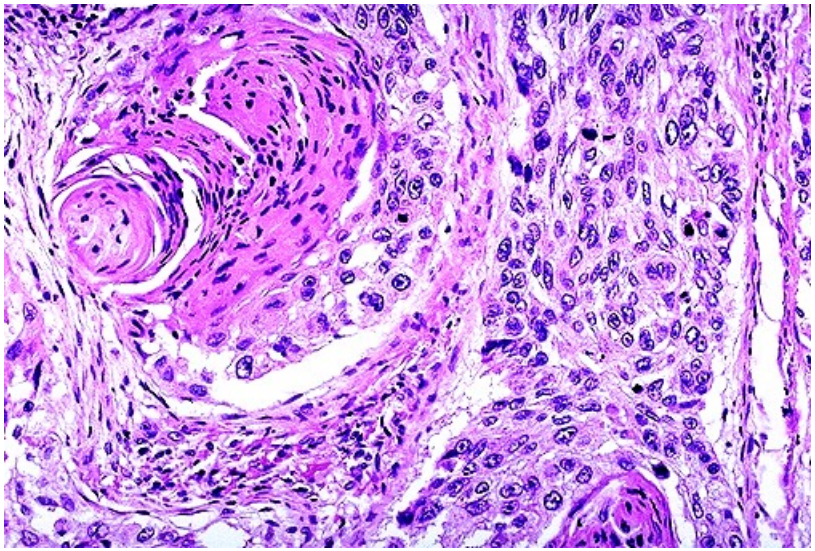


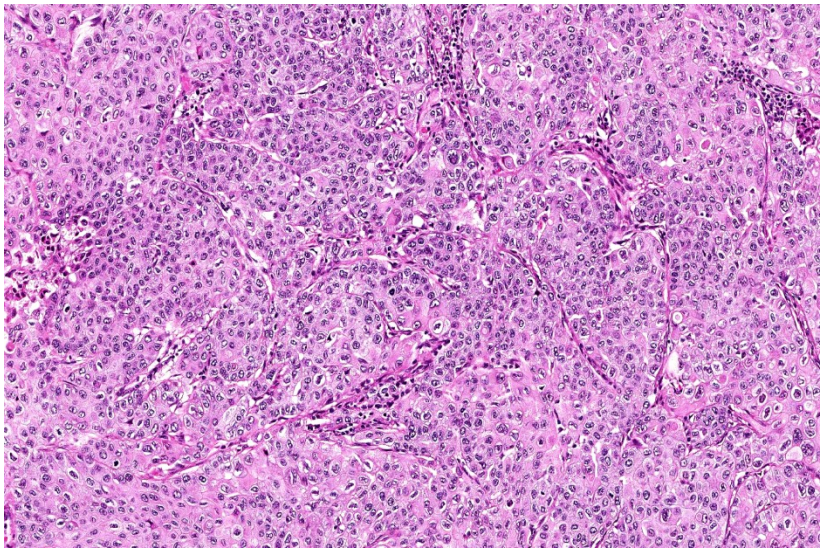




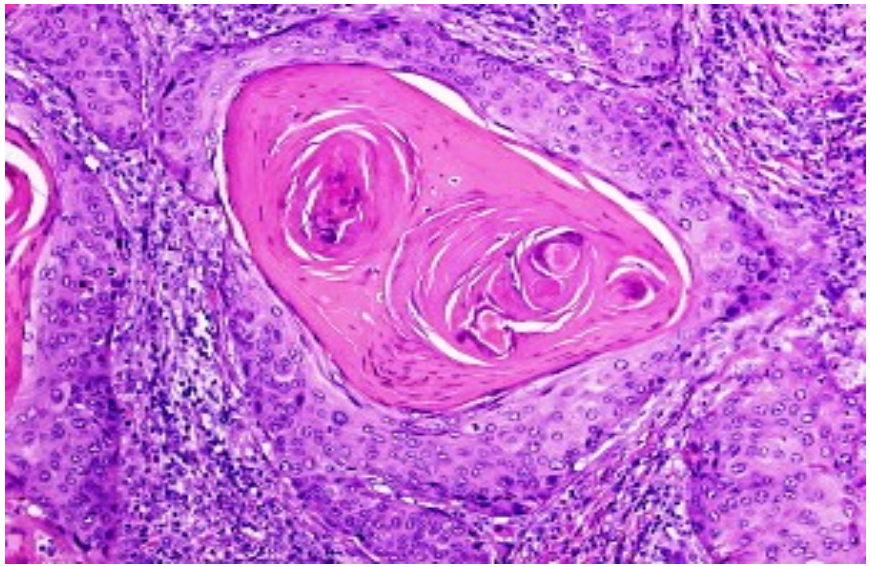
Squamous cell carcinoma

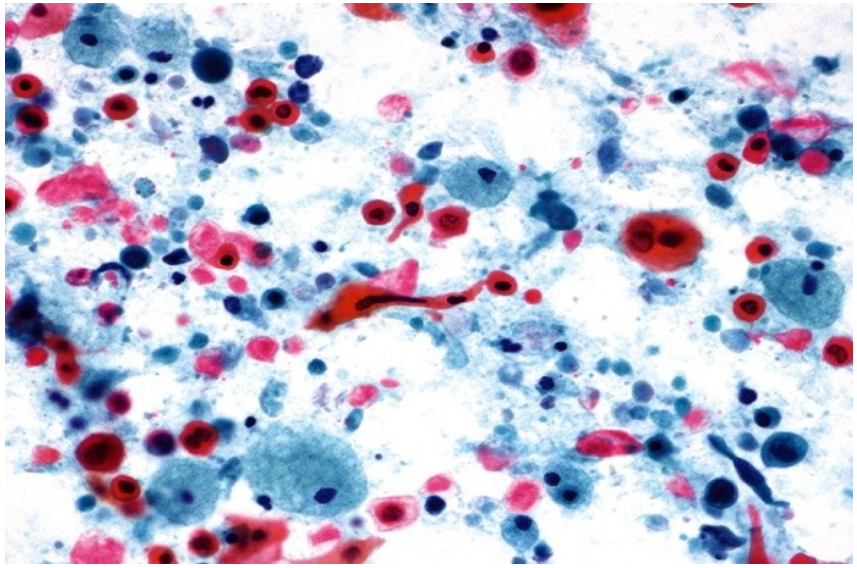


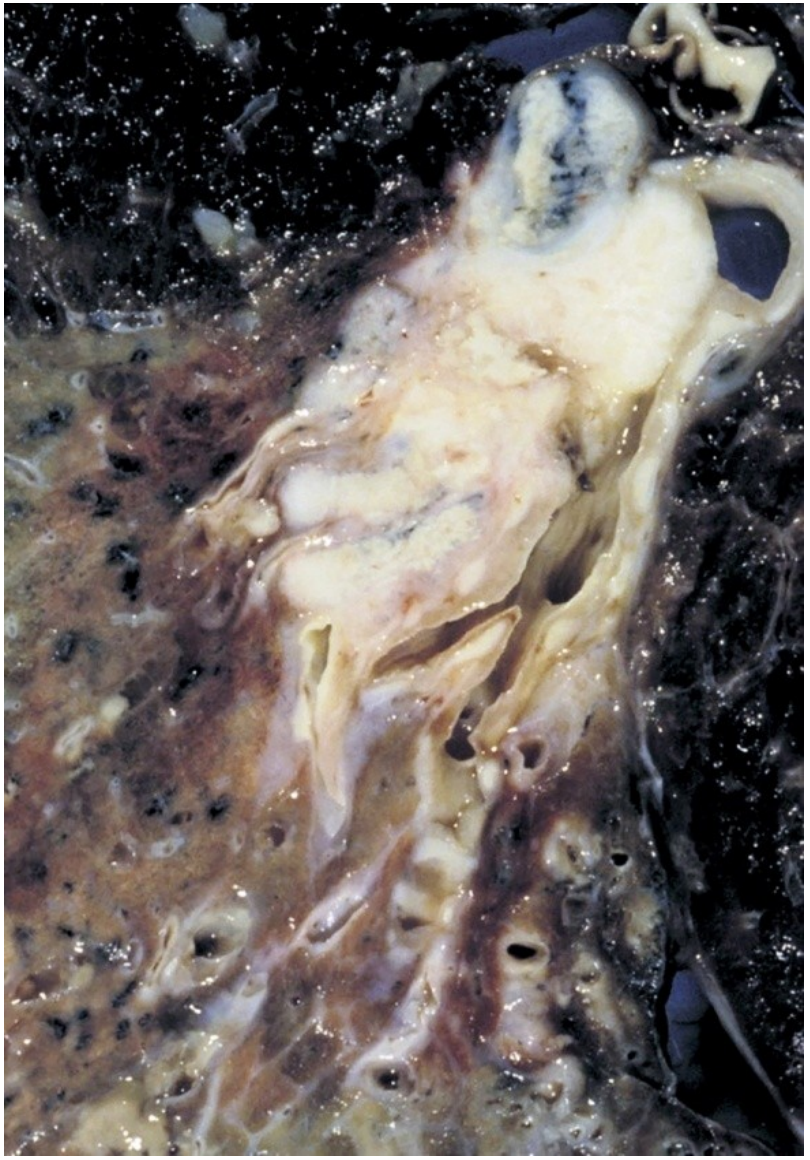




Keratinizing SCC (p40)







Pathways to lung Squamous cell carcinoma (SCC) and precancerous lesions

Mostly occur in the proximal airways

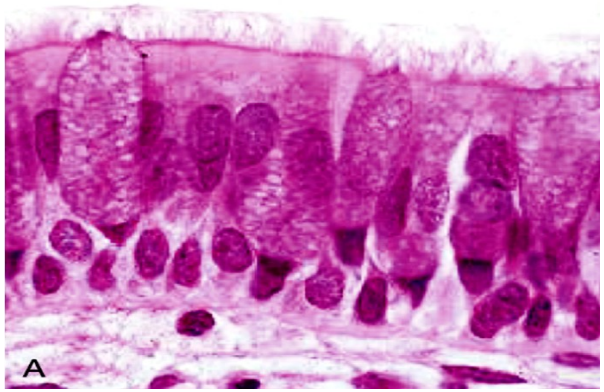
Squamous Metaplasia

Squamous Dysplasia

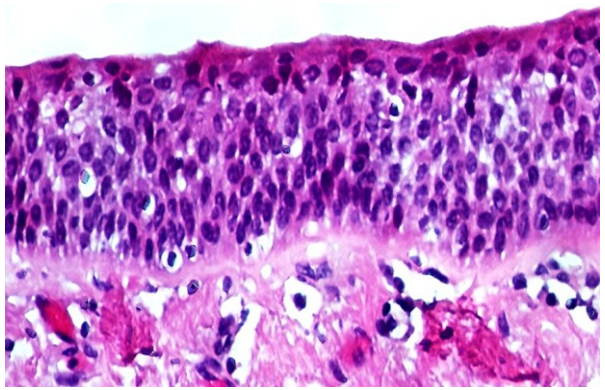
In situ SCC

Invasive SCC

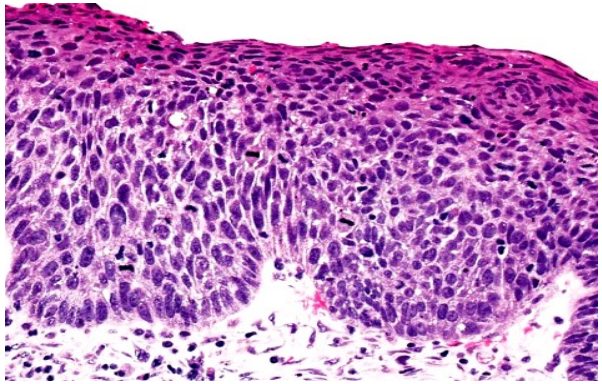
The above pathways are **non-linear** and most of the early changes are **non-obligate precancers** because they can be reversed with the cessation of the stimuli that evoked them



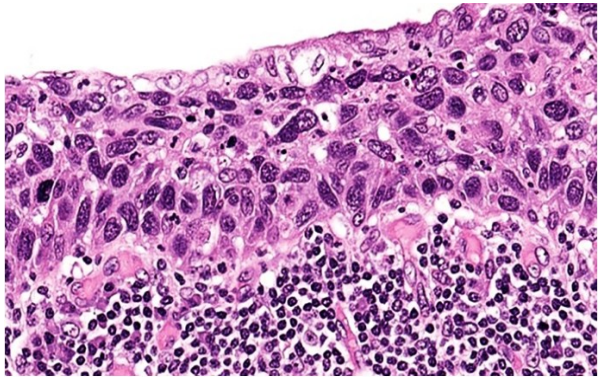
Normal epithelium



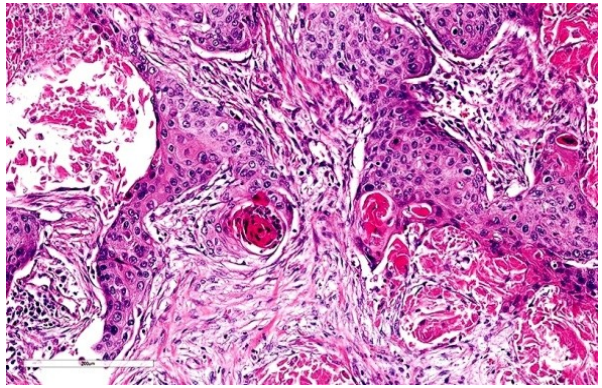
Squamous metaplasia



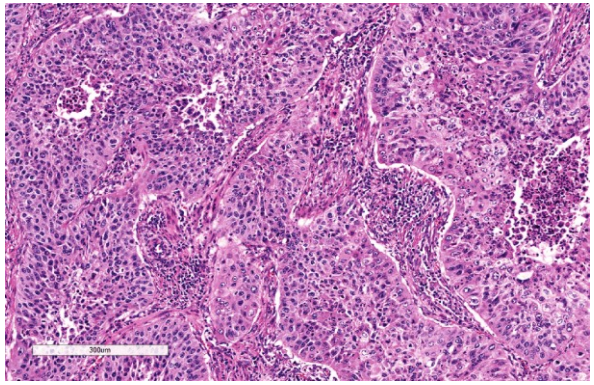
Squamous dysplasia



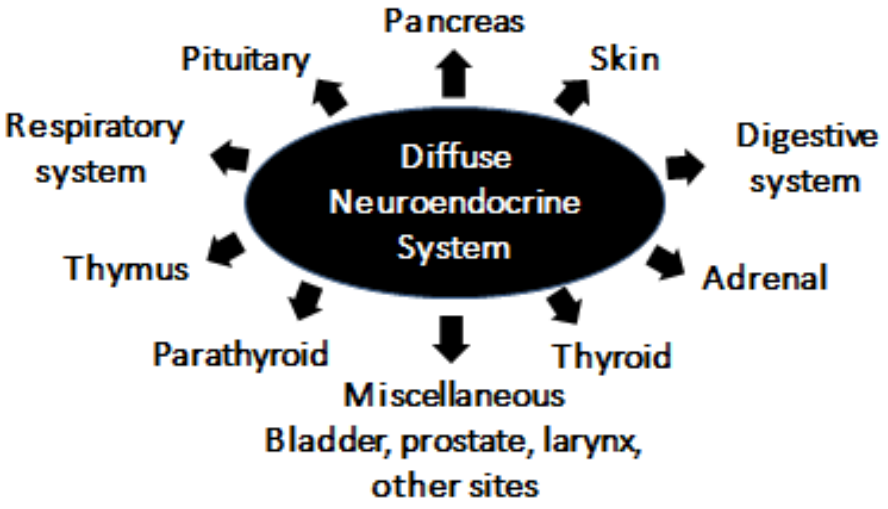
In Situ SCC

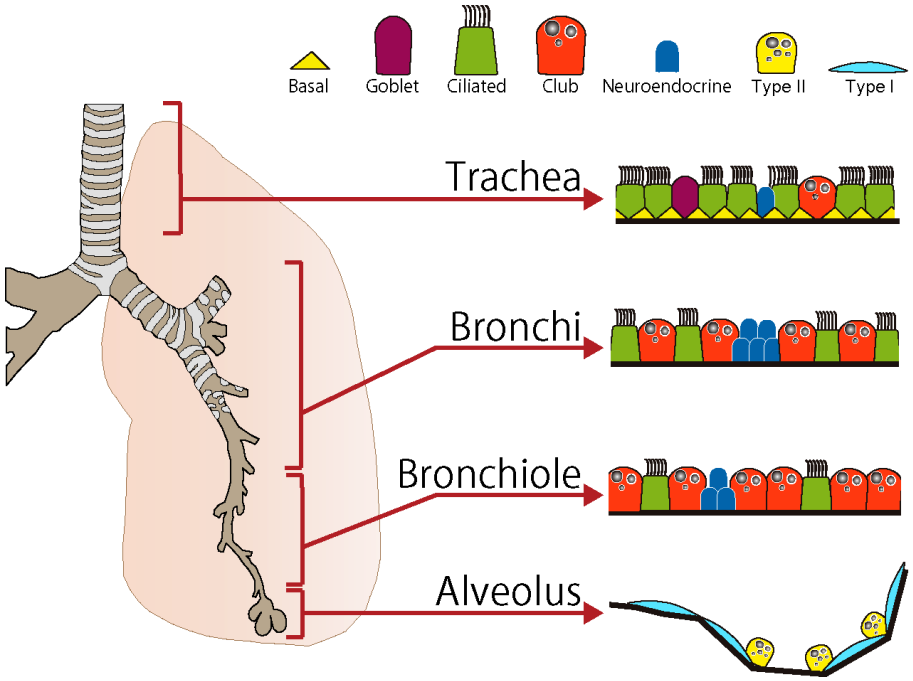


Invasive SCC



Invasive SCC





Neuroendocrine cells

Present in all epithelial site

Largest group of hormone producing cells in the body

Originate locally from stem cells

Identified by IHC for Chromogranin, Synaptophysin, CD56 or by hormones they produce

Neuroendocrine Neoplasms (NEN)	
Well differentiated	Poorly differentiated
Neuroendocrine tumors (NET)	Neuroendocrine carcinomas (NEC)
Grade 1 Typical Carcinoid <2 mitoses/2 mm^2 Ki67 <3% No necrosis **Grade 2** Atypical Carcinoid 2-10 mitoses/2 mm^2 Ki67 3%-20% Focal necrosis **Grade 3** >10 mitoses/2 mm^2 Ki67 >20% Widespread necrosis	**Small cell NEC** >30 mitoses/2 mm^2 Ki67 >30% **Large cell NEC** >30 mitoses/2 mm^2 Ki67 >30%

Mixed NE-non-NE neoplasms (MiNENs)

Endocrine component constitutes ≥30% of the neoplasm

Nikolai Kulchitsky
(1856-1925)

Carcinoid introduced in 1897 by Nikolai Kulchitsky

Carcinoid tumours have diverse histology, hormone production, molecular profile and clinical behaviour

Terminology varies by site, type and hormone secretion was problematic

Consensus meeting 2017 suggested a single classification for all neuroendocrine tumours (NET) in all sites

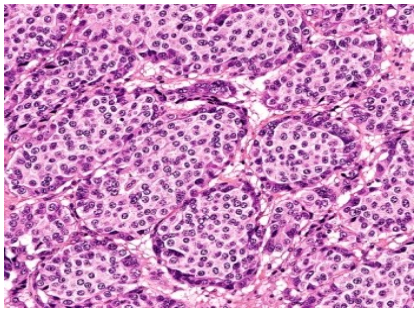
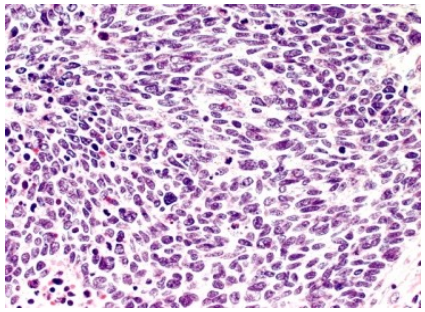
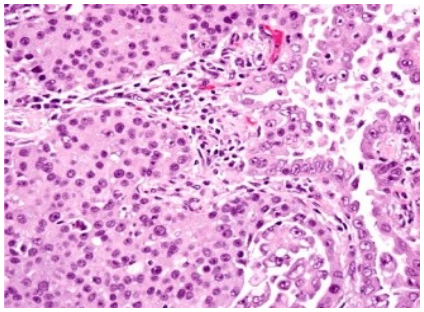
Neuroendocrine tumour to replace carcinoid tumour

Terminology adopted by WHO classification of tumours in 2019

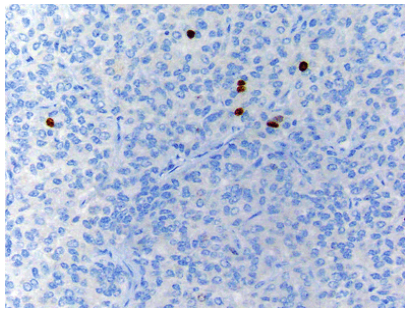
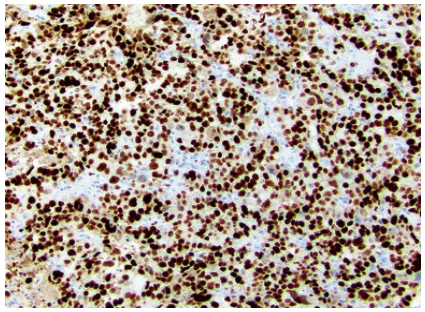
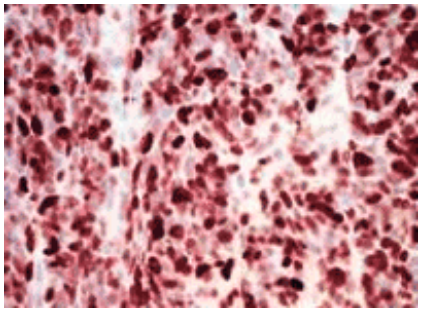
Neuroendocrine Neoplasms

	NET (Carcinoid)	Small cell NEC	Large cell NEC
Chromogranin	Pos	Pos	Pos
Synaptophysin	Pos	Pos	Pos
Cytokeratins	Pos	Pos	Pos
Mitotic index	<10 /2mm^2	>30/2mm^2	>30/2mm^2
Ki67 index (Proliferation marker)	<20%	>30%	>30%

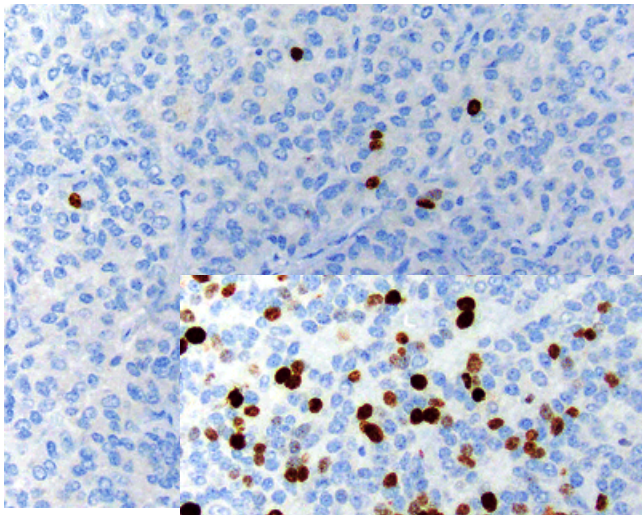
Morphology

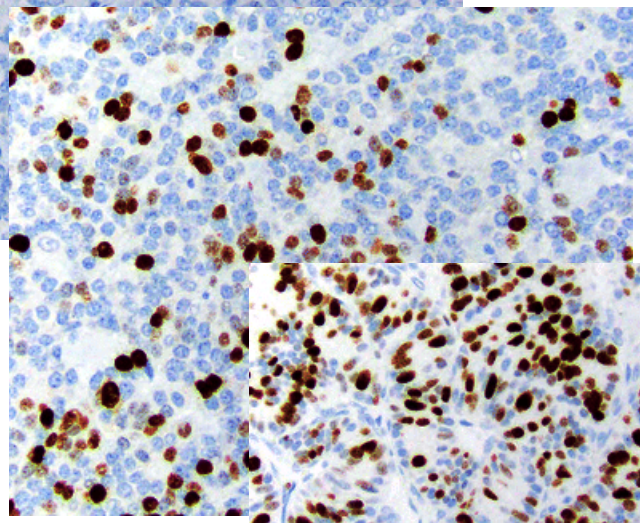
Ki67

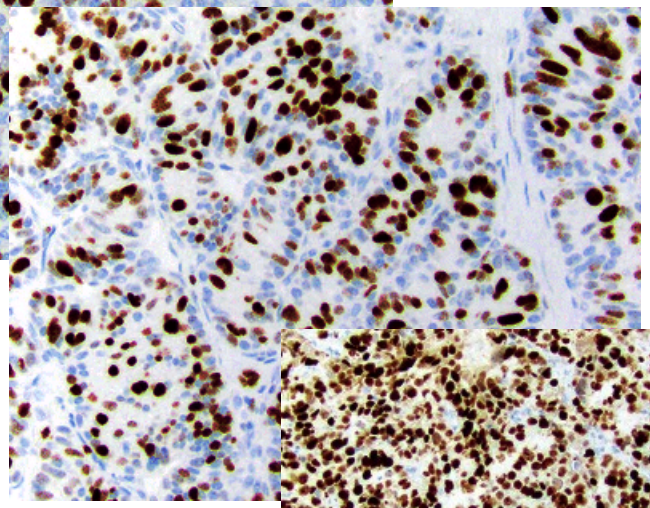
Proliferation Index (PI)
Ki67 immunostains



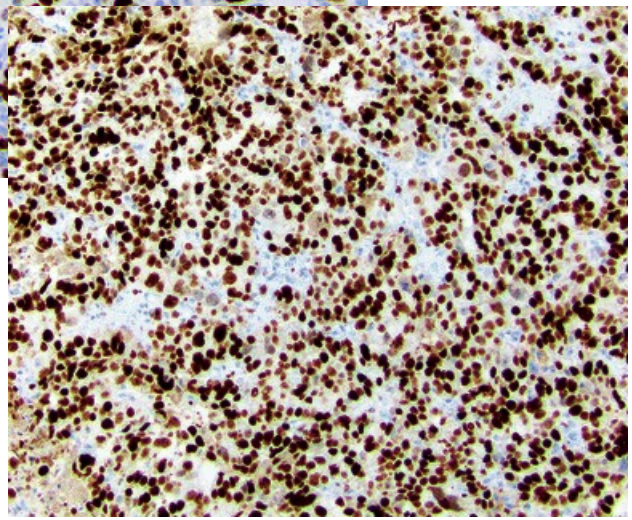
G1 NET
(Typical Carcinoid)
Ki67 <1%



G2 NET
(Atypical Carcinoid)
Ki67 10%



NEC
(Large cell NEC)
Ki67 40%



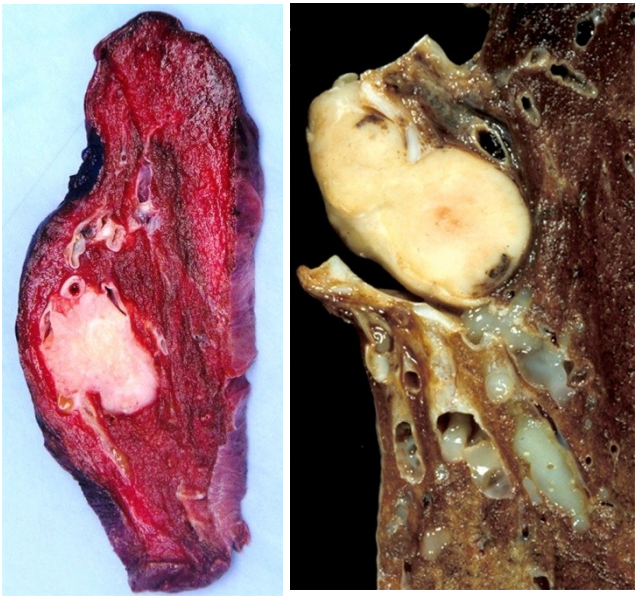
NEC
(Small Cell NEC)
Ki67 >99%

Neuroendocrine tumours (Carcinoid Tumours)

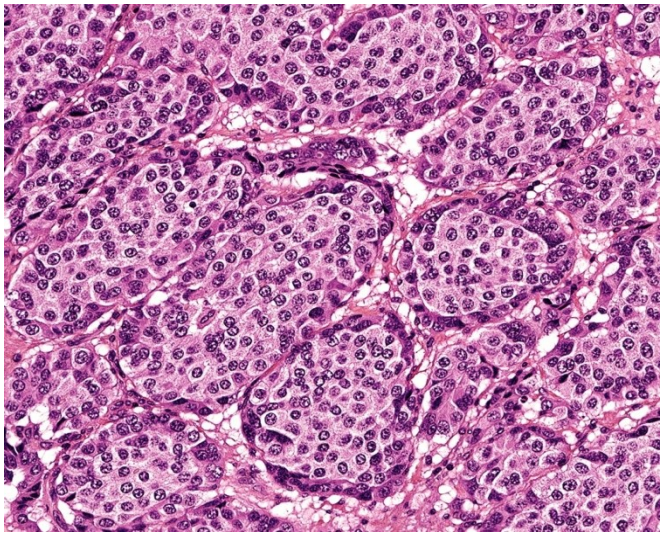
Low grade malignant tumours

NET grade 1 (typical carcinoids) has <2 mitoses/2 mm^2 and lacks necrosis

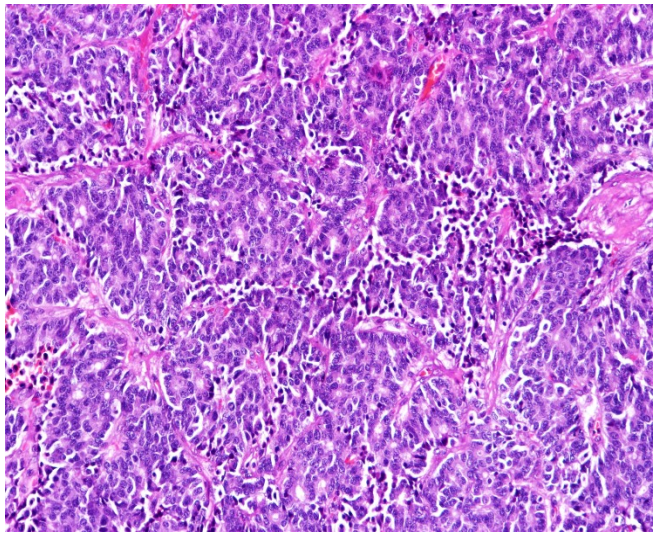
NET grade 2 (atypical carcinoids) has 2-10 mitoses/2 mm^2 or foci of necrosis



Neuroendocrine tumor (carcinoid)

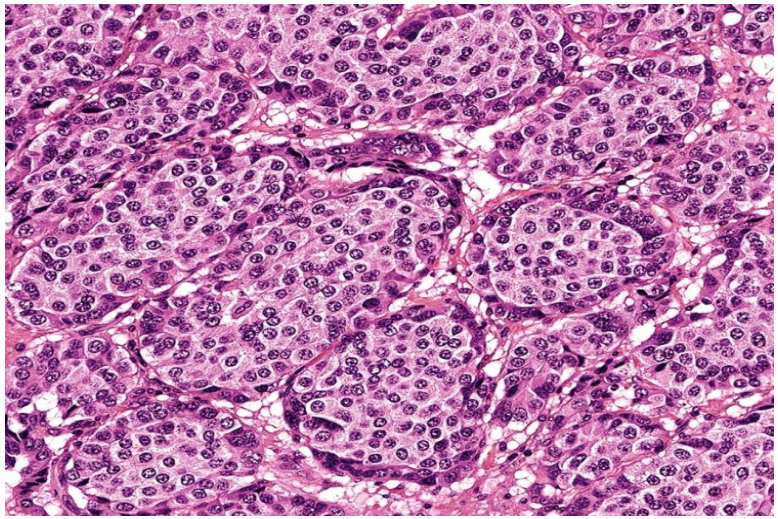


NET G1 (typical carcinoid)

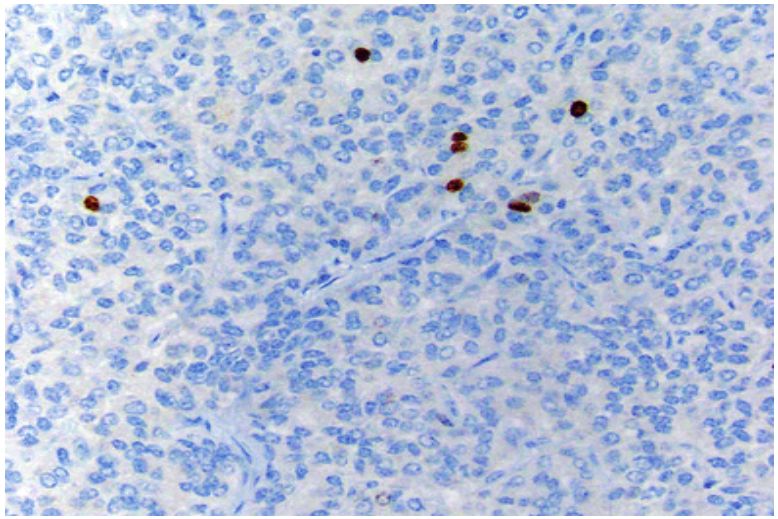


NET G2 (atypical carcinoid)

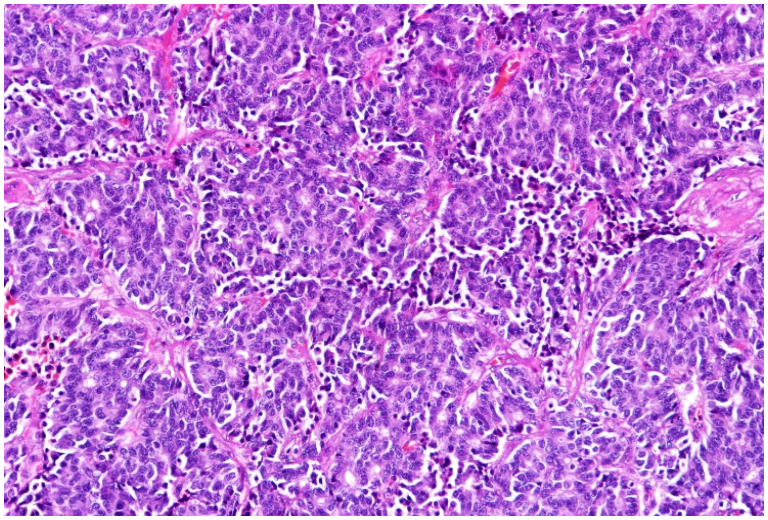
Neuroendocrine Tumours (Carcinoid Tumours)



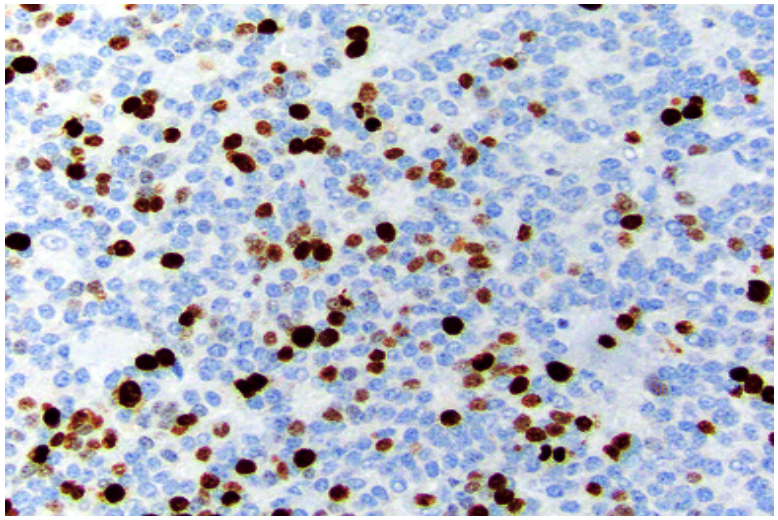
NET G1 (typical carcinoid)



Ki67 NET G1 (typical carcinoid)



NET G2 (atypical carcinoid)



Ki67, NET G2 (atypical carcinoid)

Small cell carcinoma

Highly malignant tumor

Strongest association with **smoking**

Usually **located centrally** in the major airways, frequently involving the **mediastinal lymph nodes**

Peripheral location accounts for 5%

Small cell carcinoma
Highest mutational burden among lung cancers

SCLC shares many molecular features with squamous cell carcinoma, **including p53 in up to 90%, RB in almost 100% and MYC family gene amplification**

Loss of chromosome 3p occurs in nearly all these tumors

SCLC appears as **small, round to oval blue cells** with **scant cytoplasm and finely granular chromatin**

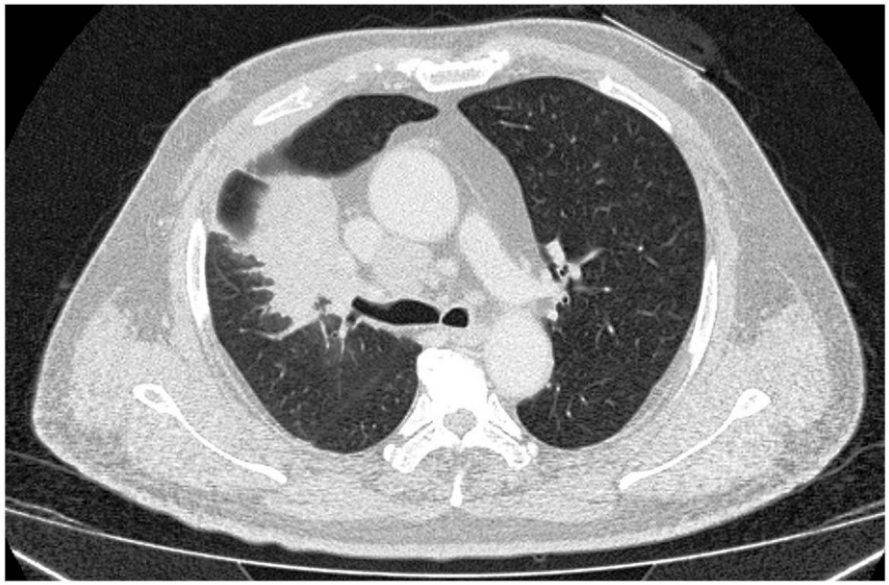
Sheets, clusters, ribbons, rosettes, peripheral palisading

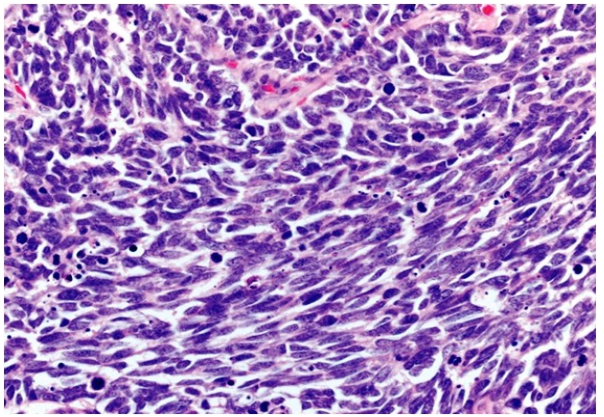
High mitotic rate, usually greater than 50 mitoses/2 mm^2

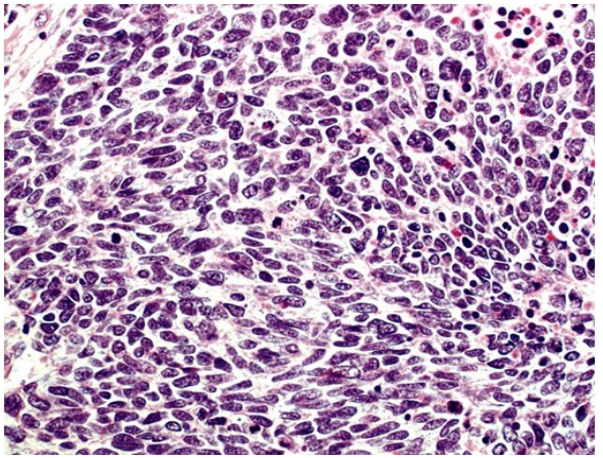
High mutational burden

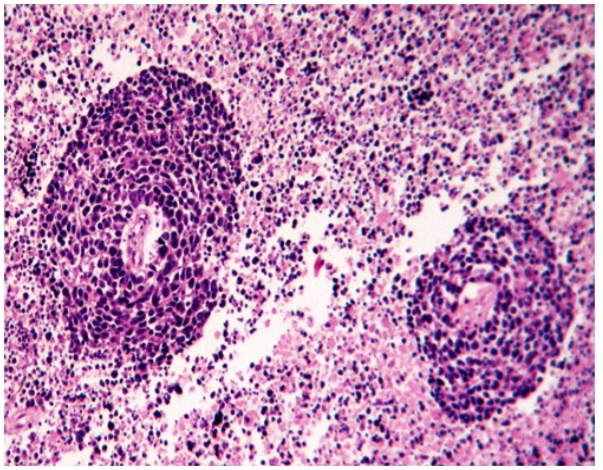
p53 and RB mutations and MYC family gene amplification

Loss of chromosome 3p occurs in nearly all these tumors

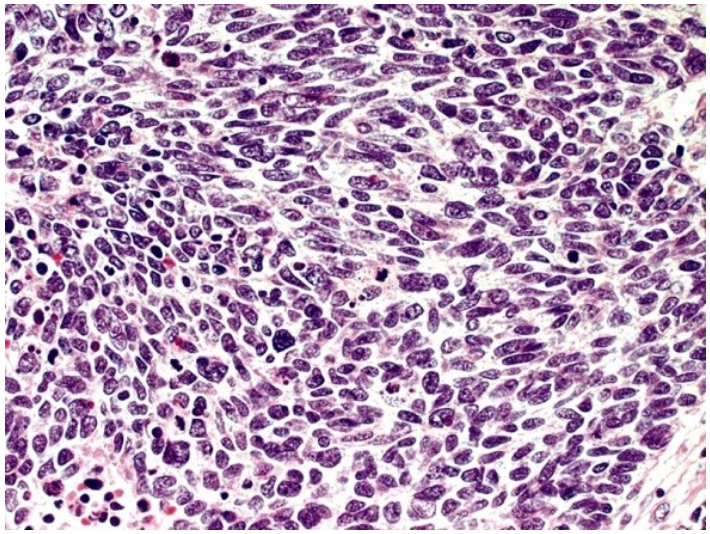


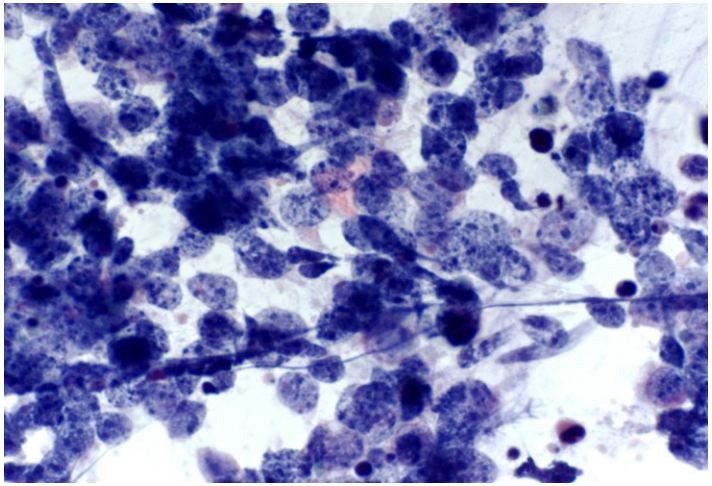


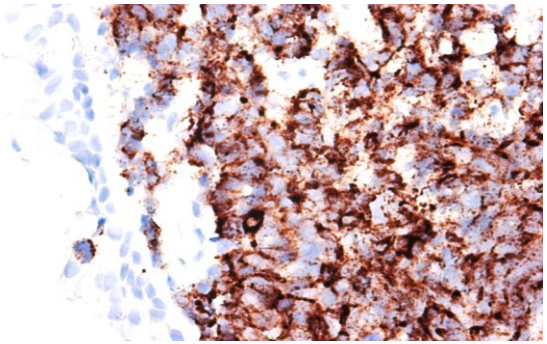




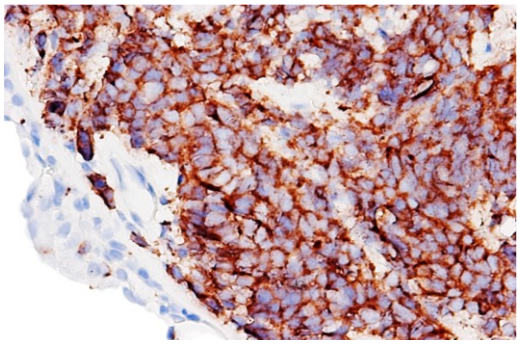
Small Cell Neuroendocrine Carcinoma (SCNEC)
Small Cell Lung Cancer (SCLC)



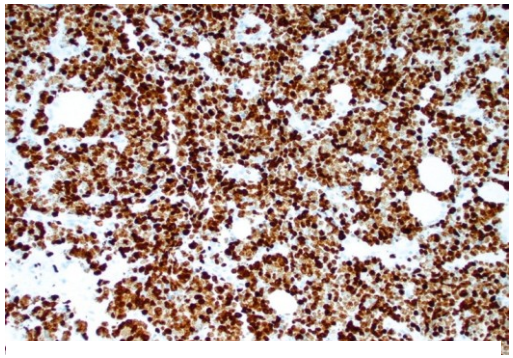




SCNEC (Chromogranin)

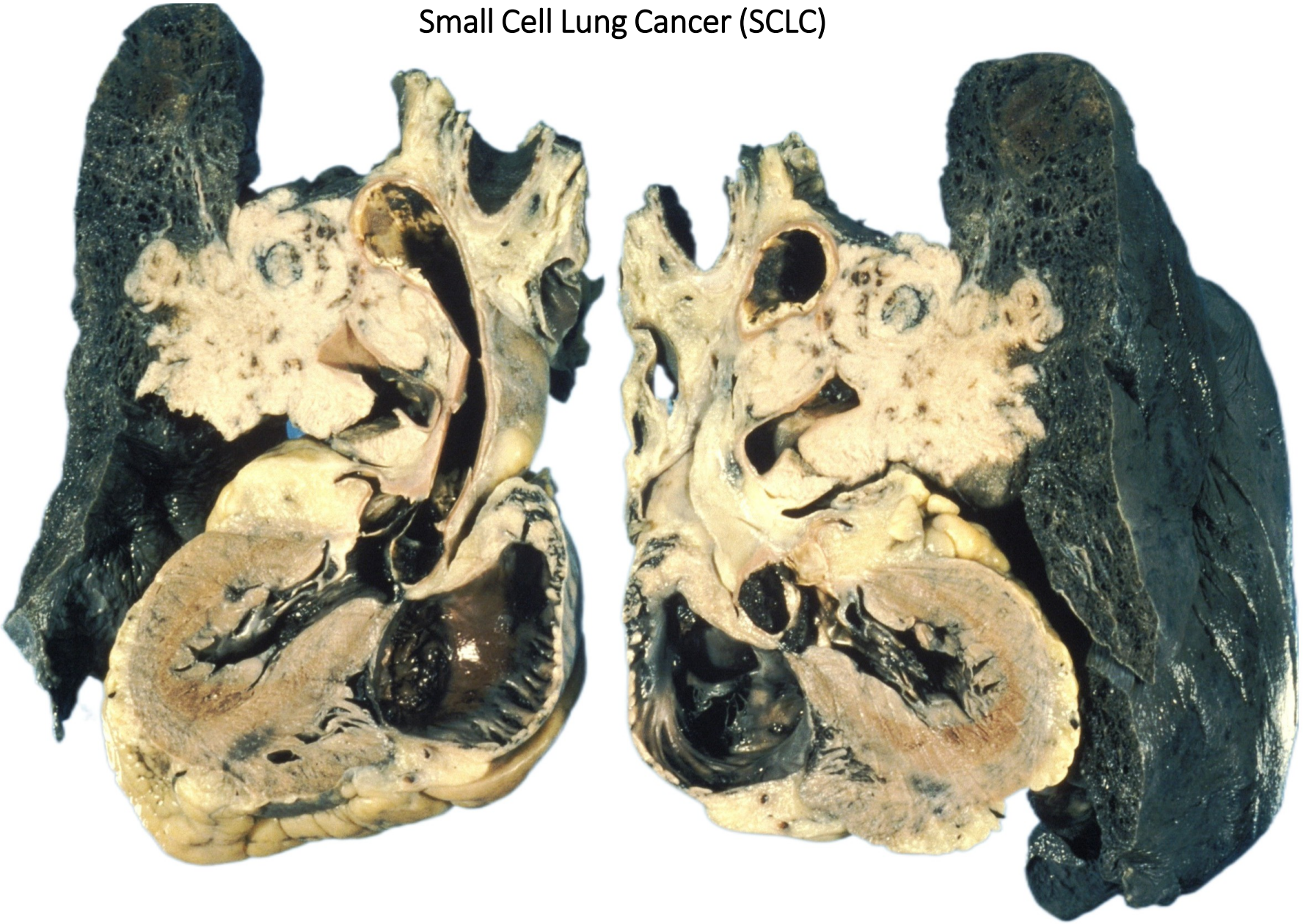


SCNEC (Synaptophysin)



Ki67

Small Cell Neuroendocrine Carcinoma (SCNEC)
Small Cell Lung Cancer (SCLC)



Large cell neuroendocrine carcinoma (LCNEC)

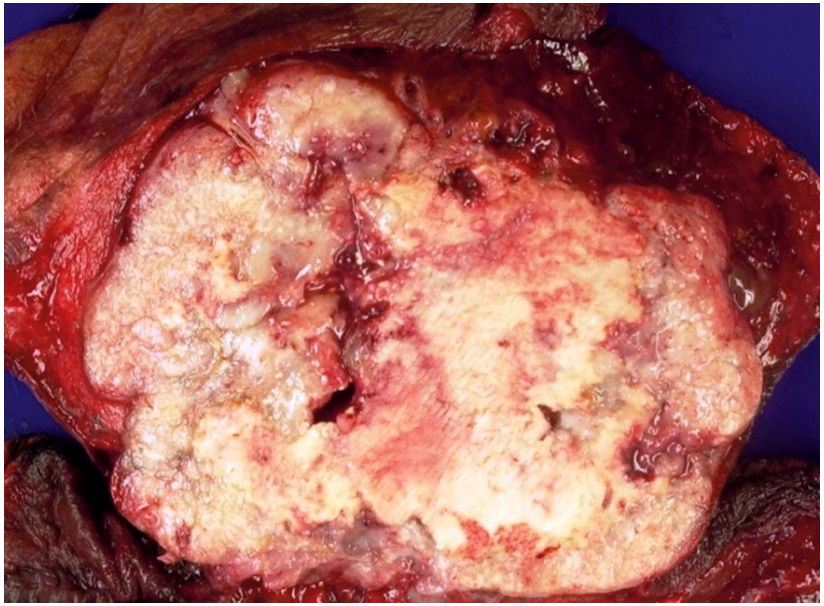
High-grade non-small cell carcinoma

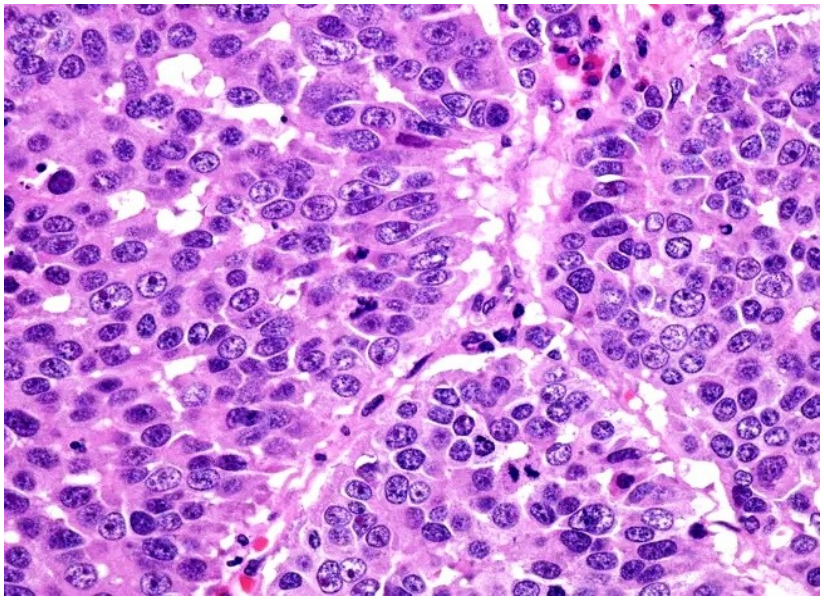
Neuroendocrine morphology

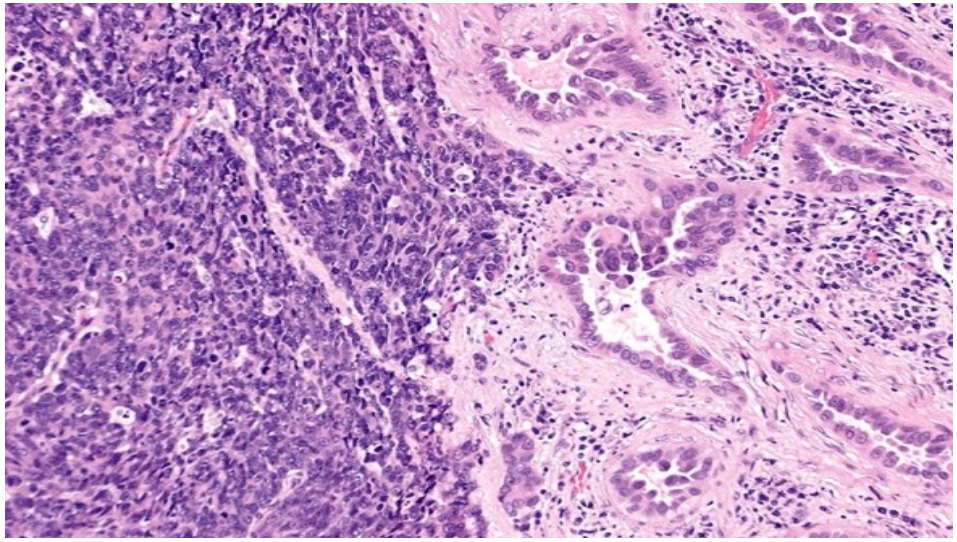
Mitotic count of >30 mitoses/2 mm^2

Ki67 >30%

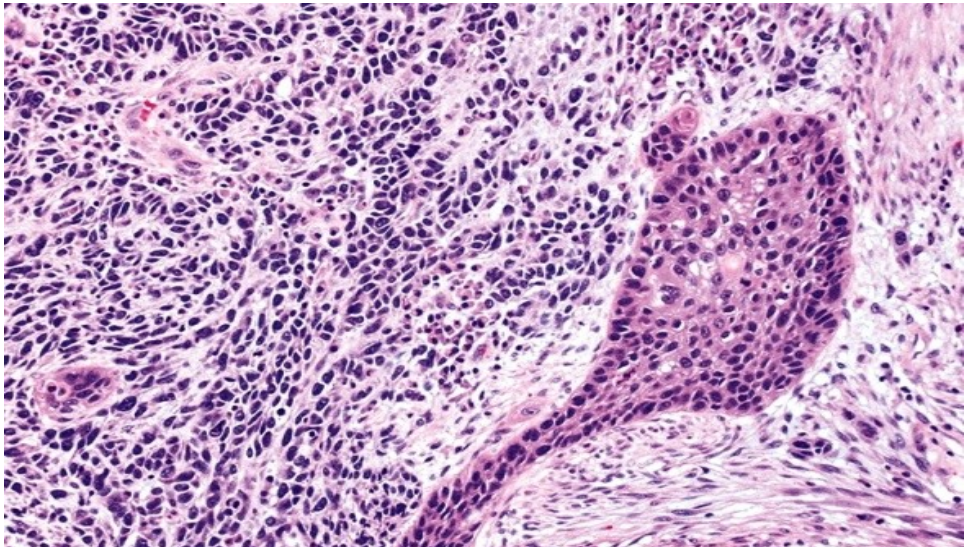
Expresses neuroendocrine markers
Chromogranin, Synaptophysin, CD56







Small cell carcinoma combined with adenocarcinoma

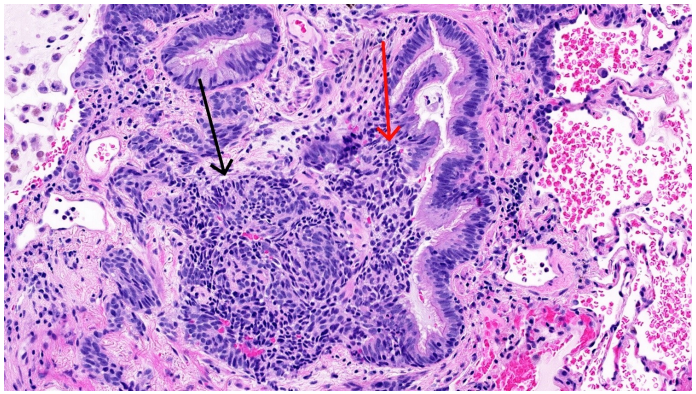


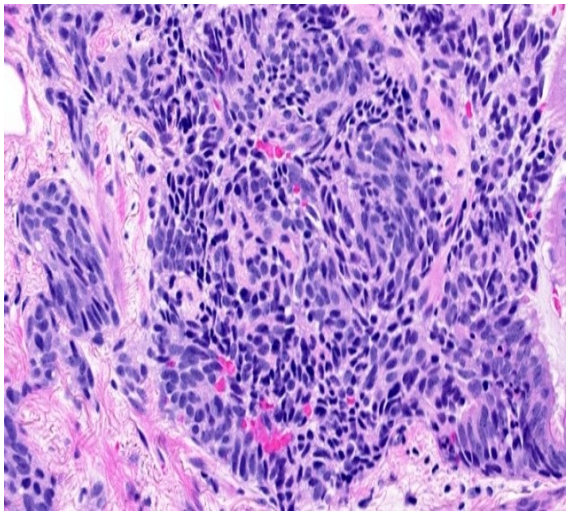
Small cell carcinoma combined with squamous cell carcinoma

Mixed NE–Non-NE Neoplasms (MiNEN)

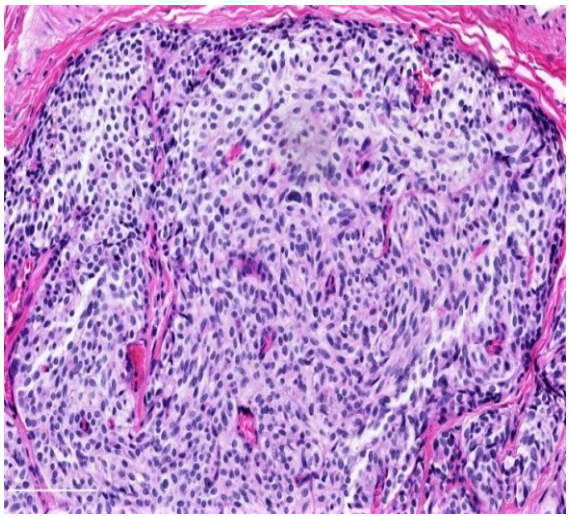
The endocrine component constitutes ≥30% of the neoplasm

Pathways to neuroendocrine neoplasms and precancers and cancers
Majority arise in the proximal airways
Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia (DIPNECH) <5mm in bronchial mucosa
Tumorlet <5mm extends beyond bronchial mucosa
Neuroendocrine Tumor (NET) >5mm with bronchial wall involvement (Carcinoid Tumor)
Neuroendocrine Carcinoma (NEC) Small Cell NE Carcinoma Large Cell NE Carcinoma

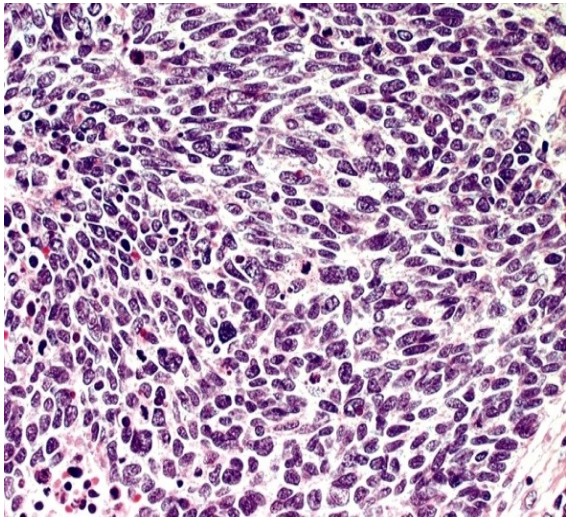




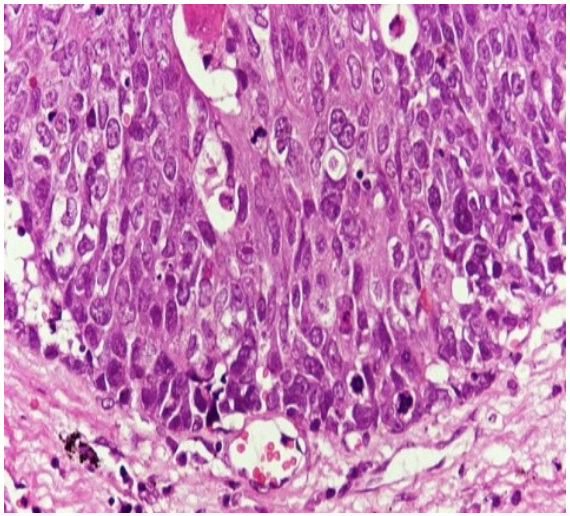
DIPNECH <5mm



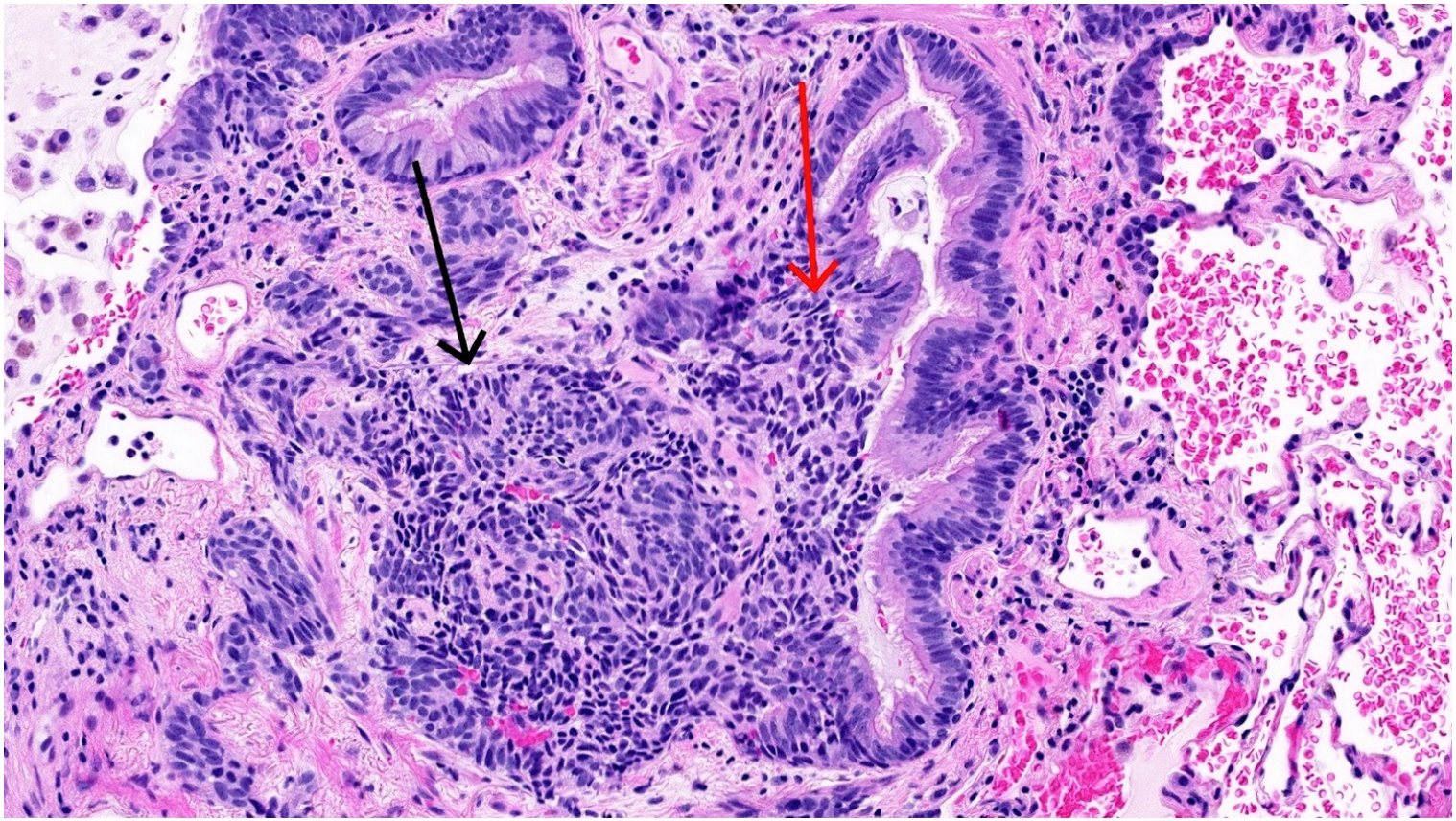
NET (CARCINOID) >5mm



SMALL CELL NEC

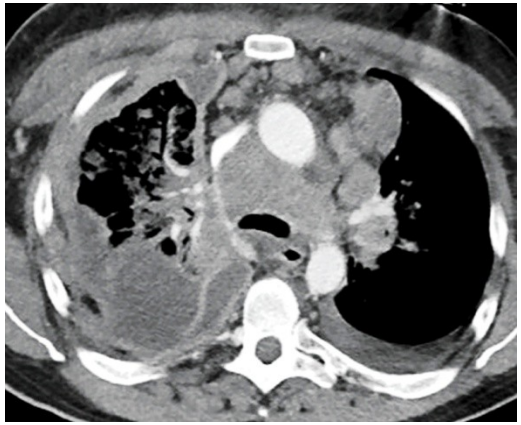
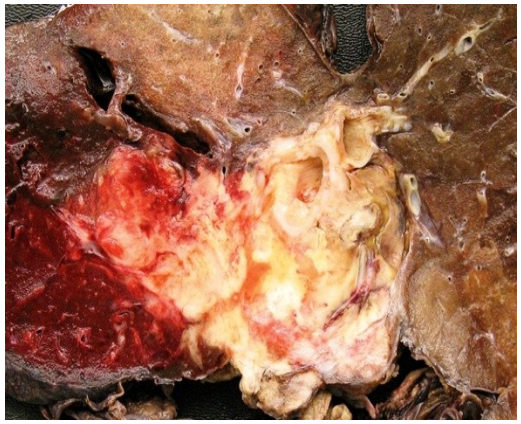
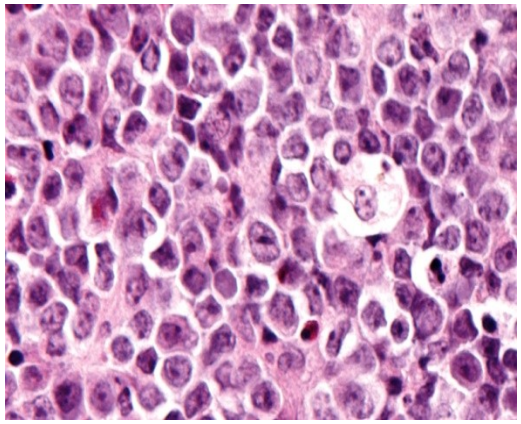
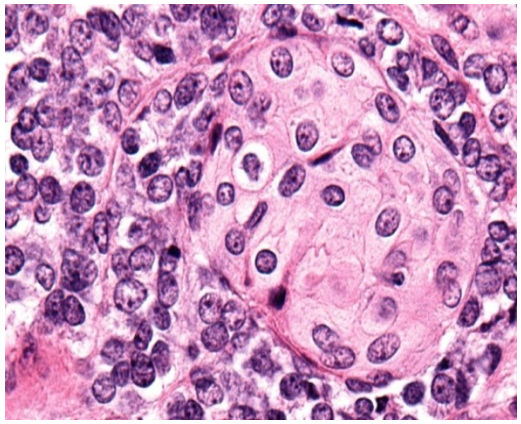
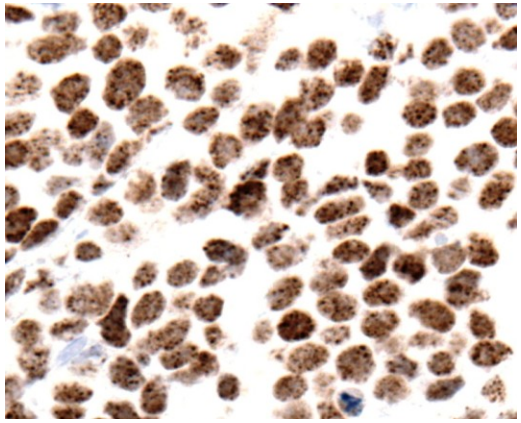
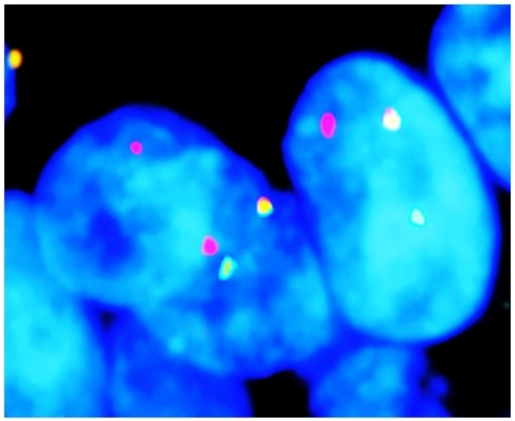


LARGE CELL NEC



Diffuse Idiopathic Pulmonary Neuroendocrine Cell Hyperplasia, <5mm in bronchial mucosa

Tumorlet <5mm extends beyond bronchial mucosa

NUT carcinoma

Nuclear Protein in Testis (NUT)

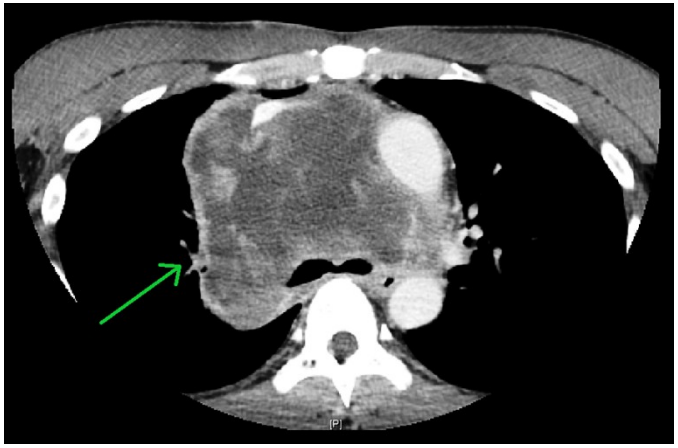
Fusion of BRD4-NUT leads to uncontrolled cell growth

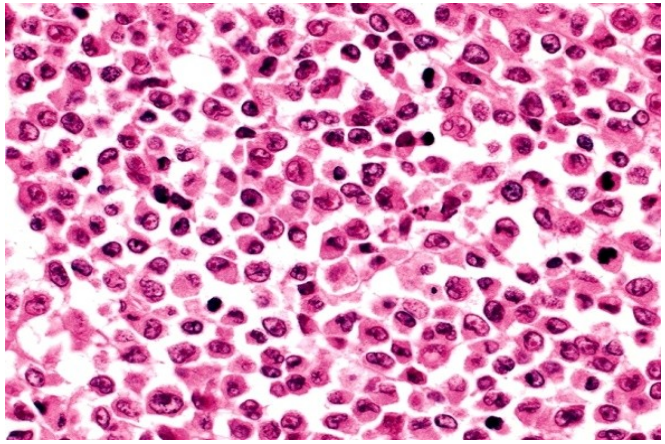
Primitive undifferentiated round cell tumour **(URC)**

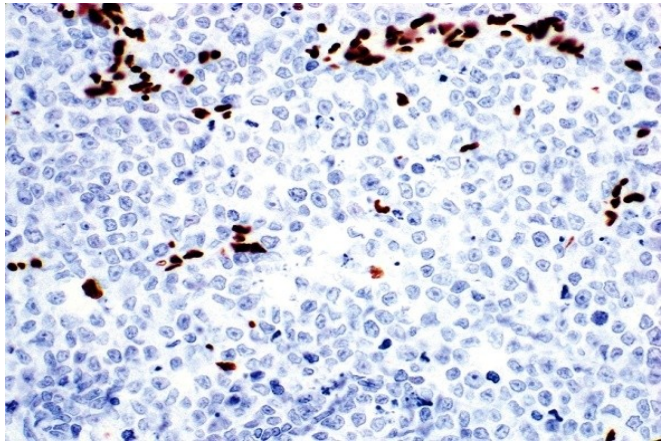
Extremely aggressive cancer with a median survival of **6 months**

Variant histological features included **basaloid, squamoid , clear cell changes, glandular differentiation and papillary architecture**

IHC for NUT protein and "split apart" signal with the fusion partner BRD4







SMARCA Deficient Tumour

SMARCA4 is a tumor suppressor gene and a subunit of SWI/SNF (SWItch/Sucrose Non-Fermentable) family

Tumor suppressor gene which regulates gene activity and repairs damaged DNA

Deficiency of SMARCA4 (SWI/SNF Related, Matrix Associated, Actin Dependent Regulator of Chromatin, Subfamily A, Member 4)

High-grade undifferentiated or rhabdoid malignant neoplasm

Involves the thorax of adults

Universally aggressive behavior and poor prognosis

Median overall survival of 6 months

<table>
<tr><th colspan="4">Neoplasms in the pleura</th></tr>
<tr><th colspan="2">Epithelial</th><th colspan="2">Mesothelial</th></tr>
<tr><th colspan="2">Morphology</th><th colspan="2">Morphology</th></tr>
<tr><th colspan="2">Most reliable IHC markers
Claudin-4, MOC-31 and Ber-EP4</th><th colspan="2">Best IHC mesothelial markers
Calretinin, CK5/6, WT-1, D2-40</th></tr>
<tr><th colspan="2">Malignant</th><th colspan="2">Benign (atypical) or malignant</th></tr>
<tr><th>Lung primary</th><th>Other primaries</th><th>Benign</th><th>Malignant</th></tr>
<tr><td>Adenocarcinoma, squamous cell carcinoma, other</td><td>Breast, GI, Kidney, Female genital, other organs</td><td>Mesothelial hyperplasia</td><td>Epithelioid, sarcomatoid, biphasic, other subtypes</td></tr>
<tr><td>Lung markers</td><td>Organ specific markers</td><td colspan="2">BAP1, MTAP and p16</td></tr>
<tr><td colspan="4">No marker is 100% specific for mesothelioma
All mesothelial markers can be positive in carcinoma subsets
Broad-spectrum cytokeratin and 2 mesothelial and 2 epithelial markers are recommended as a first-line immunopanel to determine the mesothelial lineage</td></tr>
</table>

Malignant Mesothelioma

Malignant tumor of **mesothelial cells** occurring most often in the **pleura**

Asbestos exposure in 90% of cases

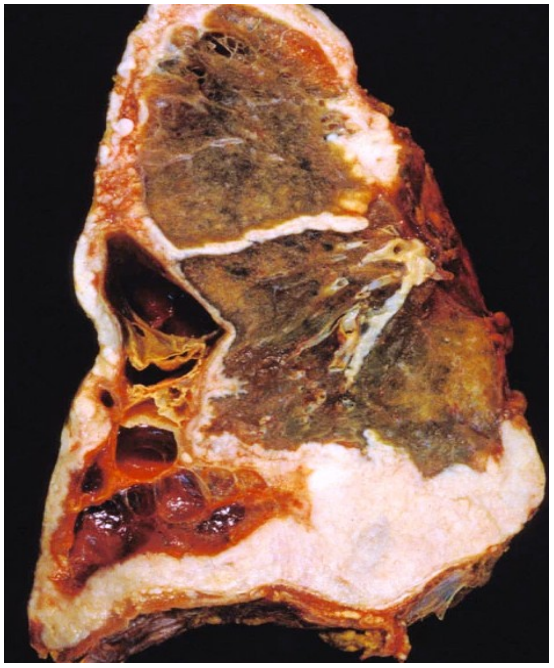
Lifetime risk in heavily exposed individuals is about **10%**

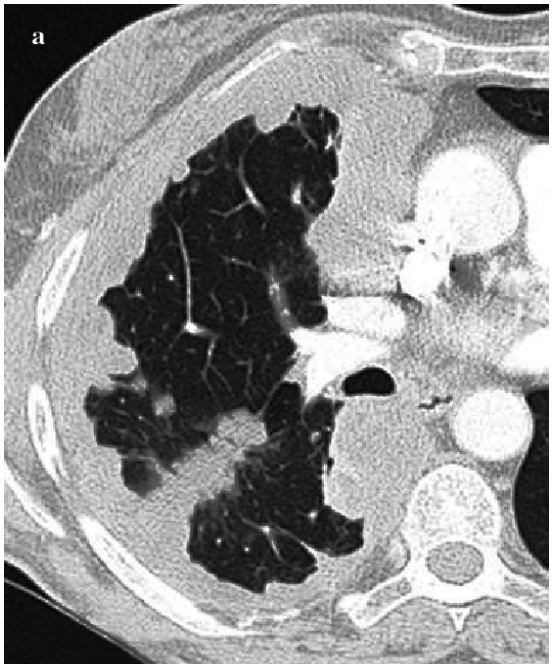
Latency period between exposure and tumor development of **30 years**

Loss of the tumor suppressor gene CDKN2A (p16) in 80% of cases

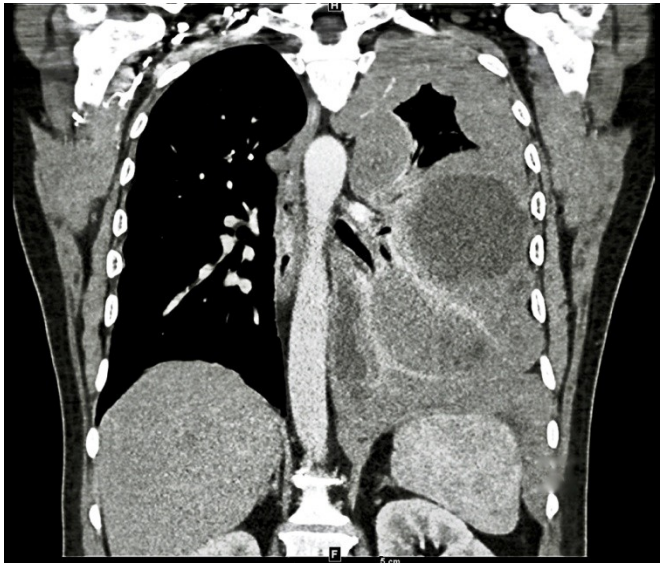
Driver mutations are also common in the **NF2 gene and BAP1**

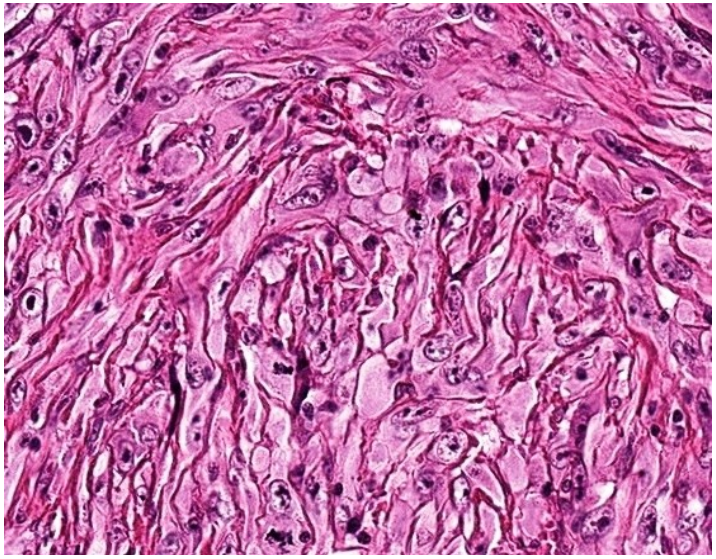
Asbestos workers who smoke are much more likely to die of **lung carcinoma** than mesothelioma



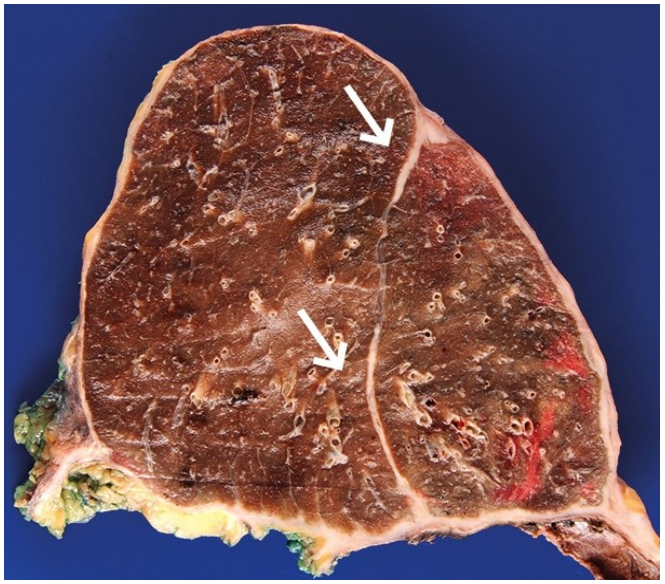


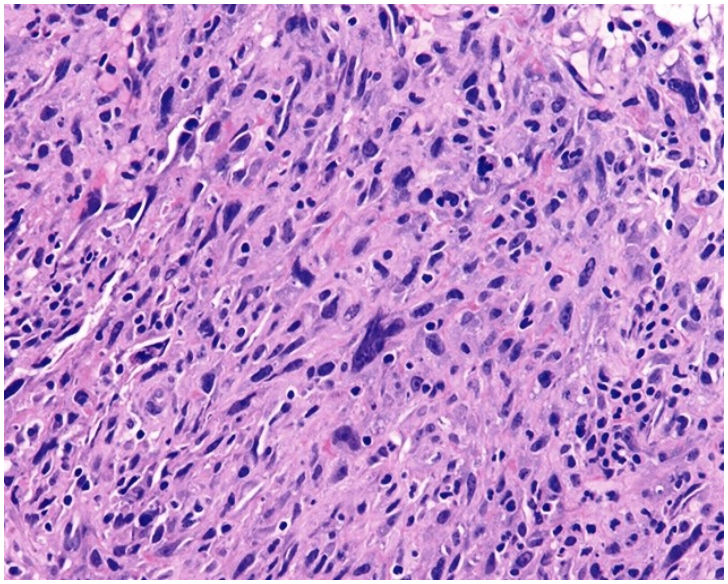
Malignant mesothelioma





Epithelioid mesothelioma





Sarcomatoid mesothelioma

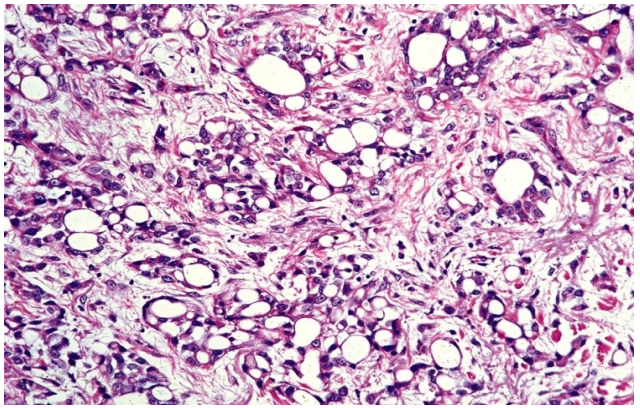
Morphology of malignant mesothelioma

Tumor spreads diffusely over the lung surface and fissures, forming an **encasing sheath**

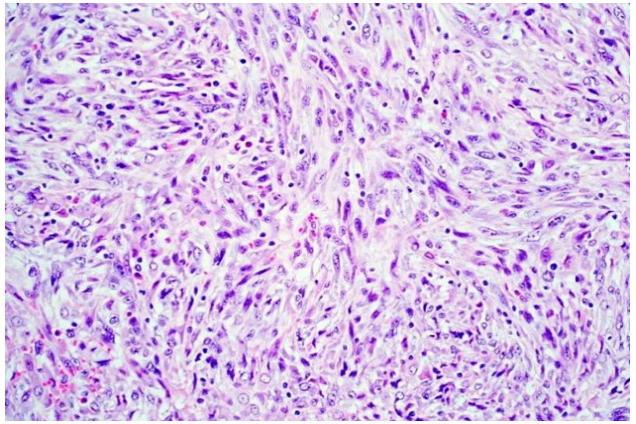
Microscopic patterns are **epithelioid** (80%), **sarcomatoid** (10%) and **mixed** (biphasic) (10%)

Epithelioid (epithelium-like) pattern form **tubules and papillary projections** resembling adenocarcinomas

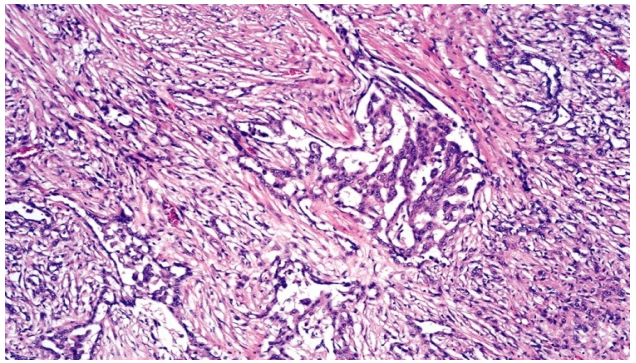
Sarcomatoid mesotheliomas are composed of **pleomorphic spindle cells**



Epithelioid mesothelioma



Sarcomatoid mesothelioma

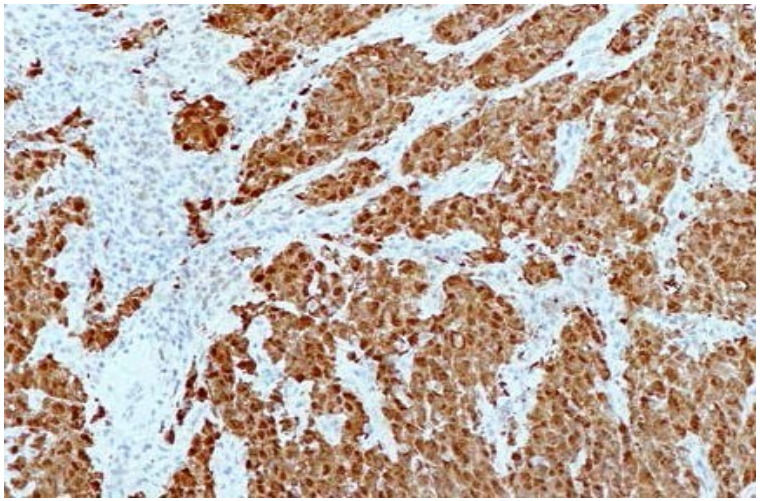


Biphasic mesothelioma

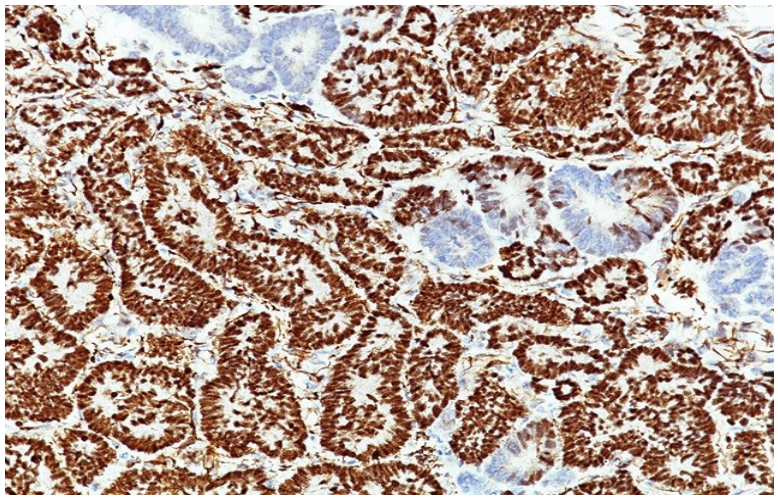
Morphology of malignant mesothelioma

Mesothelioma is positive for Calretinin, WT-1, D2-40 and cytokeratin 5/6 positivity

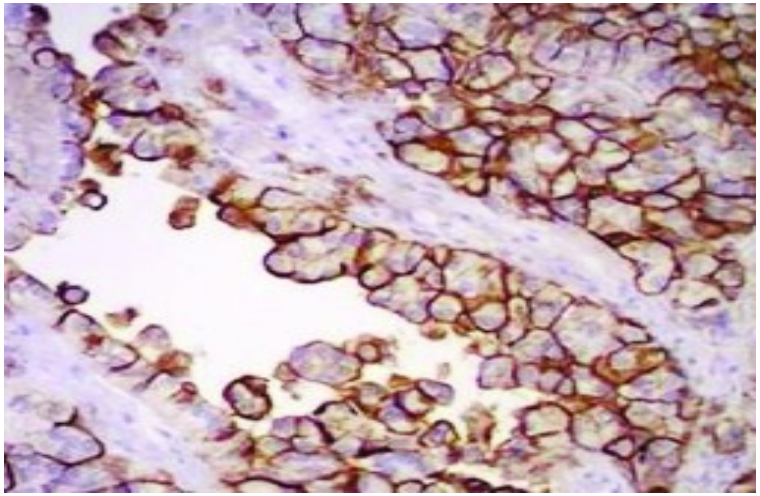
Lung adenocarcinomas are positive for CEA, TTF-1, Napsin-A and Claudin 4



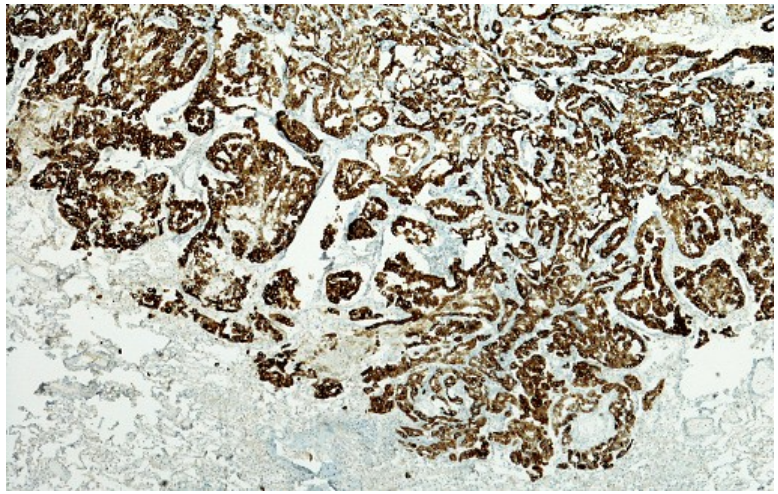
Calretinin (mesothelioma)



WT-1 (mesothelioma)



D2-40 (mesothelioma)



CK5/6 (mesothelioma)

Atypical (reactive) mesothelial proliferation Versus epithelioid mesothelioma		
Biomarker	**Atypical mesothelial proliferation**	**Epithelioid mesothelioma**
BAP1	Pos	Neg
MTAP	Pos	Neg
CDKN2 (p16)	Pos	Neg

BAP1 (BRCA1-Associated Protein 1) loss has 70% sensitivity and 100% specific for malignancy in mesothelial lesions

MTAP (Methylthioadenosine Phosphorylase) loss has 50% sensitivity and 100% specific for malignancy in mesothelial lesions

CDKN2A (Cyclin-Dependent Kinase Inhibitor 2A) and its protein product p16 homozygous deletion of CDKN2A has 70% sensitivity and 100% specificity for malignancy in mesothelial lesions

IHC stain	Mesothelioma	Adenocarcinoma
Calretinin	Positive	Negative
D2-40 (podoplanin)	Positive	Negative
WT1	Positive	Negative
Cytokeratin 5 / 6	Positive	Negative
Claudin 4	Negative	Positive
MOC31	Negative	Positive
TTF1	Negative	Positive
Napsin A	Negative	Positive
B72.3	Negative	Positive
BG8	Negative	Positive
CEA (monoclonal)	Negative	Positive
BerEP4	Negative	Positive
BAP1	Loss in 60% of epithelioid MM	Retained

Mesothelioma markers: Calretinin, D2-40, WT1 and CK5/6

Adenocarcinoma markers: Claudin 4, MOC31, TTF1, Napsin A, CEA, BerEp4 and BAP1

Organ specific IHC markers

Lung ADC	CK7/CK20 +/-, TTF1 +, Napsin A +
Breast CA	GATA3, GCDFP-15, ER, mammaglobin
Colorectal ADC	CDX2, SATB2
Prostate ADC	PSA, PAP, NKX3.1
RCC	PAX8, PAX2, vimentin, RCCma, CD10
Urothelial CA	GATA3, uroplakin-II
Thyroid CA	Thyroglobulin, PAX8, TTF1
Adrenal cortical CA	SF-1, inhibin, Melan-A
Hepatocellular CA	Arginase-1, Hep-Par1, glypican 3, AFP
Pancreatic ADC	CK17, MUC5AC, S100P
Ovarian serous CA	PAX8, WT1, inhibin, β-catenin
Ovarian mucinous CA	PAX8, MUC5AC, β-catenin
Endometrium CA	ER, PAX8, vimentin
Endocervical CA	PAX8, p16, HPV

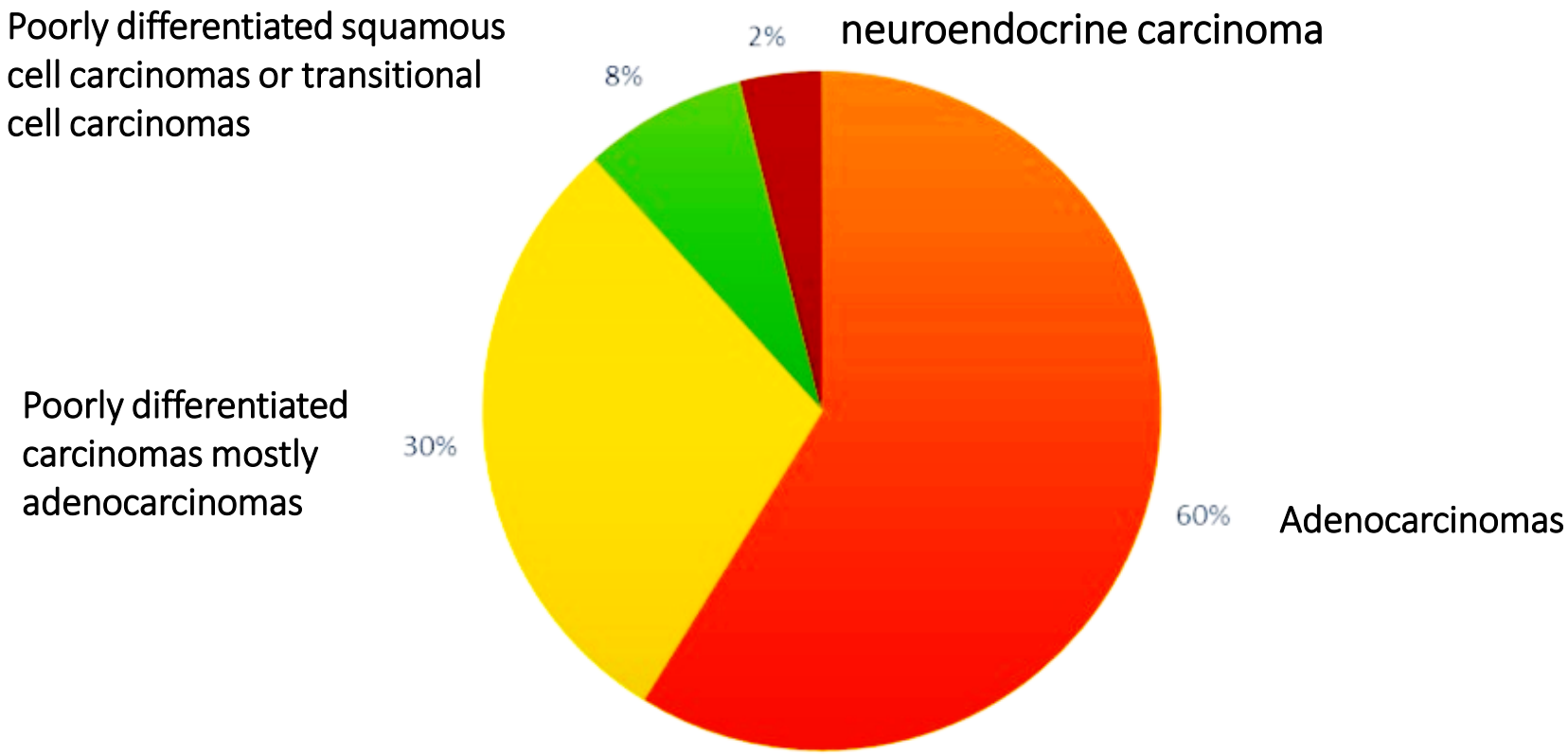
Cancer of unknown primary (CUP)

Widespread metastatic cancer without an identifiable primary site

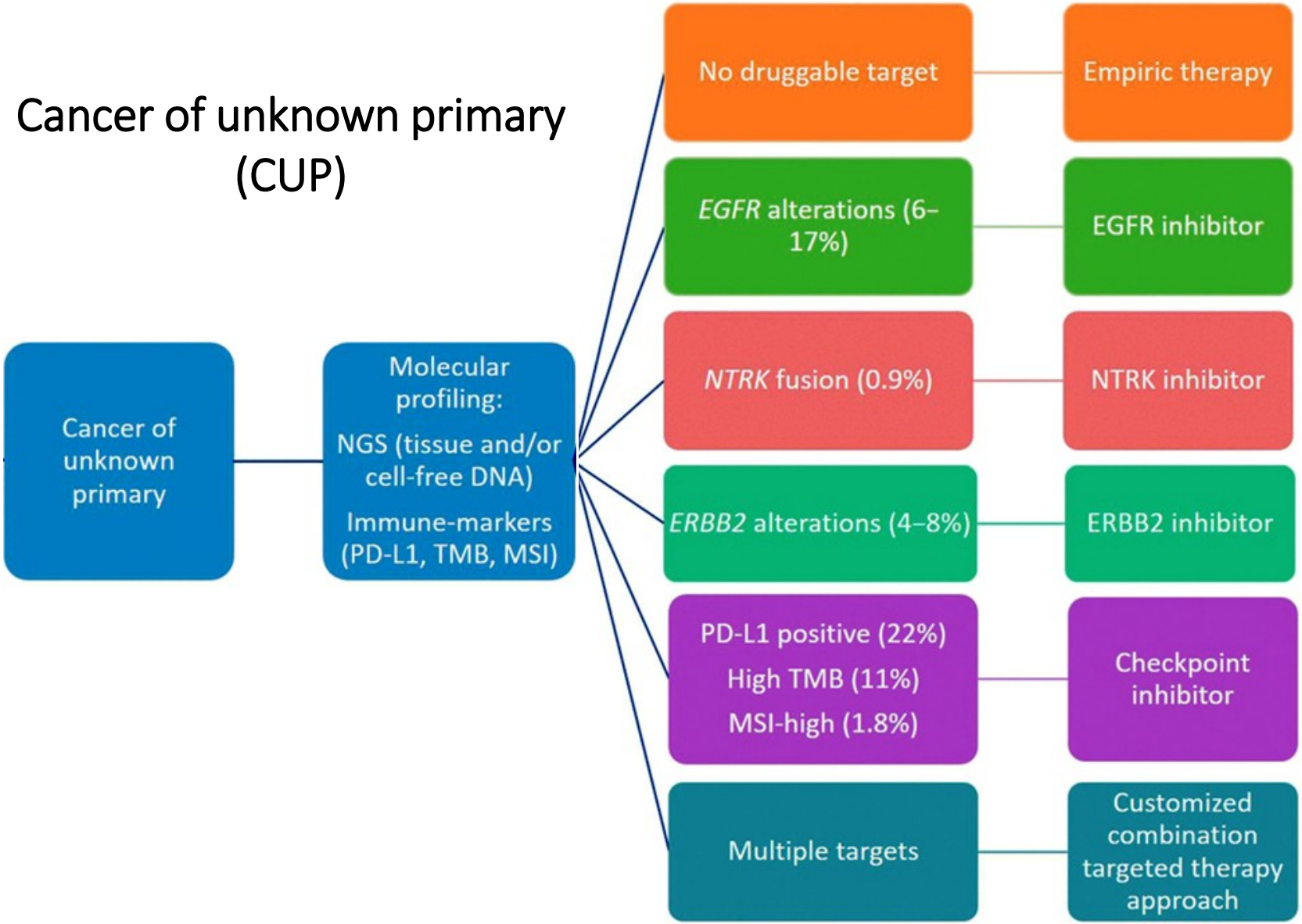
Accounting for up to 5% of a new cancer diagnosis (6th most common malignancy)

Currently less frequently diagnosed due to improvement in detection of the primary

Cancer of unknown primary (CUP)



Cancer of unknown primary (CUP)



Conclusion

The integration of **prognostic** and **predictive biomarkers** into lung cancer management has transformed patient care

Prognostic markers inform disease course and survival irrespective of treatment

Predictive markers guide targeted and immunotherapies, optimizing outcomes

Prognostic Markers

Predict disease progression and survival, **independent of treatment**

Clinical indicators

ECOG performance status and smoking status

Pathological indicators

Tumor stage, histological differentiation

Molecular markers

Mutations in p53, RB1, KRAS, STK11, PIK3CA are associated with worse prognosis

- Aggressive behavior
- Poor survival
- Resistance to targeted therapy and to immunotherapy

Molecular Predictive Markers

Predictive markers identify patients likely to **benefit from specific therapies**

Targeted Therapy:

EGFR mutations, ALK rearrangements, ROS1 rearrangements, BRAF, MET alterations, RET rearrangements, HER2 mutations

Immunotherapy:

PD-L1 expression, Tumor Mutational Burden (TMB) and dMMR/MSI-High correlate with better immunotherapy response.

STK11/KEAP1 Mutations:

Associated with immunotherapy resistance

Chemotherapy/Radiotherapy:

Low ERCC1 and high RRM1 predict better response to platinum-based and gemcitabine therapies, respectively

Low Thymidylate Synthase (TS) levels correlate with improved pemetrexed response in non-squamous NSCLC

Role of pathology in patient care in lung cancer

- Morphological diagnosis and degree of differentiation
- Immunohistochemical (IHC) confirmation
- Rule out metastasis when lung markers are aberrant
- Determine molecular profile of the tumour
- Prognostic and predictive information

Molecular alteration in lung cancer

Genetic Alteration	ADC	SCC	SCLC
Mutation			
BRAF	5%	0%	0%
EGFR			
Caucasians	15%	<1%	<1%
Asians	45%	<5%	<5%
KRAS			
Caucasians	35%	<5%	<1%
Asians	5%	<5%	<1%
P53	35%	60%	>90%
RB	10%	10%	>90%
PIK3CA (p16)	<5%	10%	**<5%**
Amplification			
EGFR	5%	10%	1%
HER2	5%	1%	1%
MET	5%	5%	1%
MYC	5%	5%	25%
FEGFR	5%	20%	1%
Gene rearrangement			
ALK	5%	1%	0%
RET	1%	0%	0%
ROS	1%	0%	0%
NTRK	1%	0%	0%

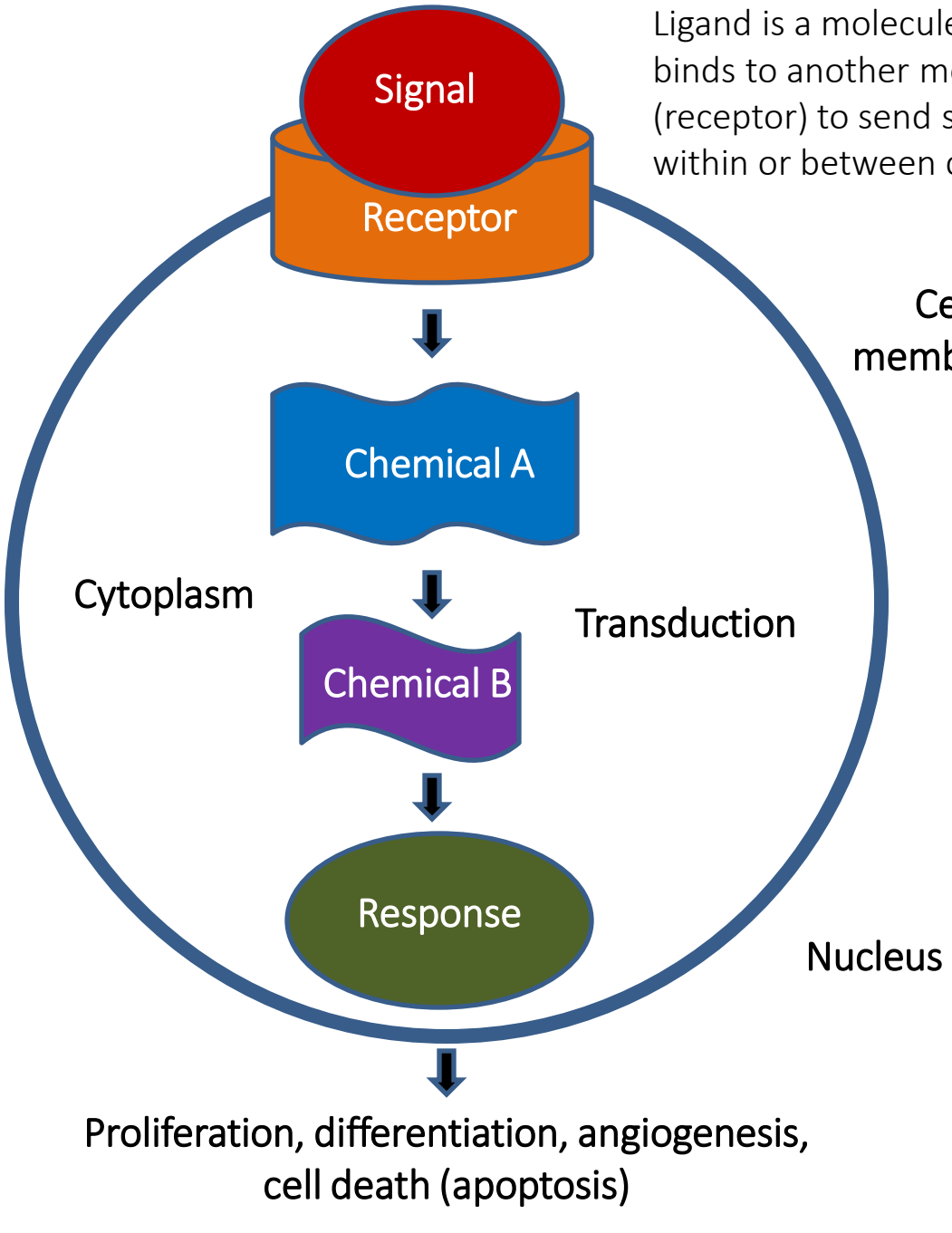
Signaling Pathways

Group of molecules working together to control cell function

Regulate biological processes through multiple cellular mechanisms

Promote cell survival, growth and cell cycle progression

Dysregulation
Abnormal activation of signal transduction can predispose to **cancer**



KRAS and BRAF

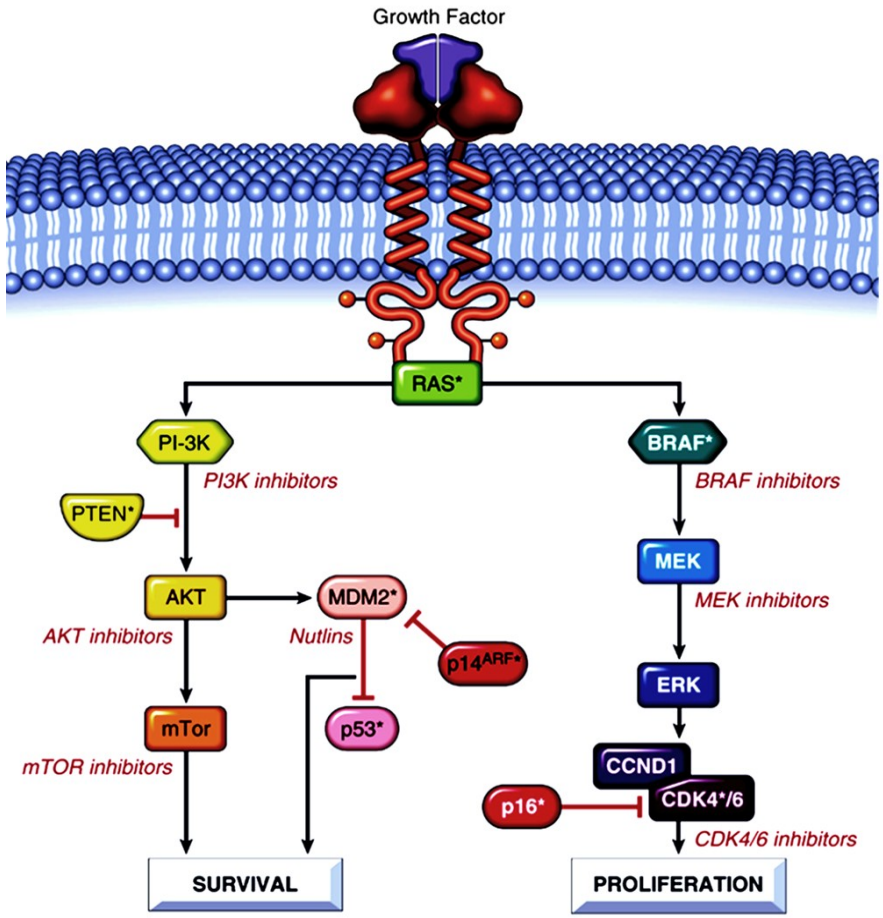
KRAS and BRAF are oncogenes involved in cell growth, proliferation, differentiation and survival (key role in oncogenisis)

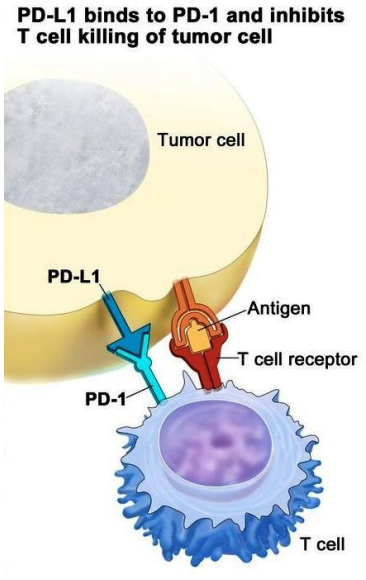
BRAF is downstream of KRAS

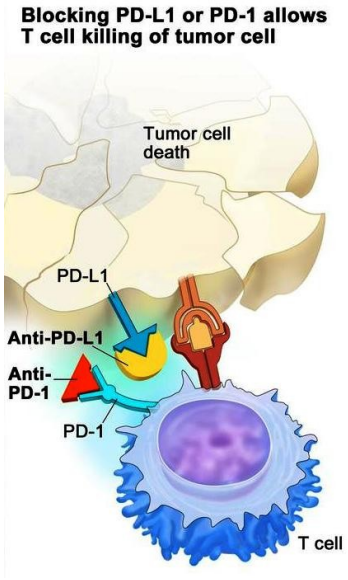
KRAS is one of the most important players in human cancers

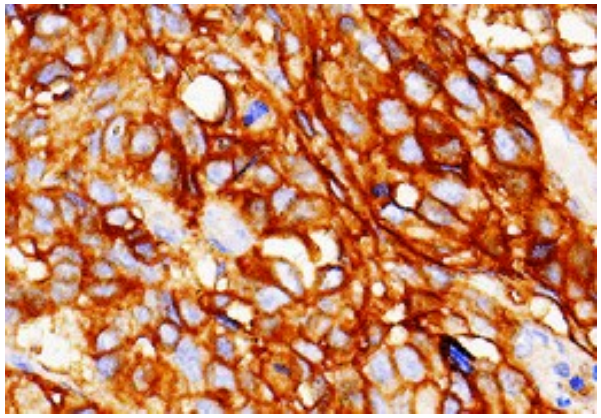
Activating of RAS (RAS-GTP) occurs in 90% of pancreatic tumors, 35% of lung cancers and 40% of CRCs

BRAF is mutated in at least 10% of metastatic CRC (V600E)









Esophageal cancer
PD-L1 positive (IHC)

Checkpoint Proteins

PD-1: Receptor found on immune cells.
PD-L1: Ligand present on the surface of some tumor cells.
Ligand: Molecule that binds to a receptor to send signals within or between cells.

Checkpoint proteins act as "off switches" for the immune system.
When PD-1 binds to PD-L1, it sends signals that **reduce immune activity.**
This **prevents tissue damage** but can also **stop the immune system from killing tumor cells.**

PD-L1 is amplified in many cancers (80% of esophageal SCC and 60% of gastric and gastroesophageal junction cancers, especially MSI-H and EBV subtypes)

Blocking PD-L1 from binding to PD-1 using checkpoint inhibitors (anti-PD-L1 or anti-PD-1) **reactivates T cells, enabling them to attack and kill tumor cells**

The Future of Lung Cancer Care

Lung cancer treatment is rapidly evolving, offering new hope through early detection, advanced diagnostics, precision medicine and innovative therapies.

Early Detection

Low-dose CT screening for high-risk individuals
Liquid biopsies for non-invasive cancer detection

Personalized Medicine & Emerging Therapies

Targeted treatments based on **genetic mutations (EGFR)**
Sotorasib for previously untreatable **KRAS mutations**
Checkpoint inhibitors and CAR-T cell therapies

Overcoming Treatment Resistance

New drug combinations targeting multiple pathways
Manipulation of the tumor microenvironment for novel solutions

Improving Access

Expanding global collaboration to ensure equitable treatment availability

Outlook

Advancements in precision medicine and global collaboration are transforming lung cancer care, moving it toward a **more manageable and potentially curable disease.**